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A VARIANT OF THE HOFSTÄTTER–CULLEN SIGN IN INTRA-ABDOMINAL HEMORRHAGE FROM ECTOPIC PREGNANCY*

With a Note on the Mechanism of Its Production

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ORDINARILY one thinks of Cullen's sign — when it is thought of at all — as the blue navel of ectopic pregnancy. Actually, other diseases can produce the phenomenon, it often appears away from the umbilicus, other colors are as frequent as blue, and it was first described by Hofstätter.[1] Cullen's[2,3] classic description and Brödel's[4] painting of his case, however, taught the world to look for the sign and English-speaking nations to call it Cullen's.

The sign can be caused by intra-abdominal hemorrhage from any source and is counterfeited by other nonbloody fluids. After ectopic pregnancy, the next most frequently reported cause is acute pancreatic necrosis, but upon meeting the phenomenon one should consider everything capable of producing colored intra-abdominal fluid, whether in the peritoneal cavity, retroperitoneally or in the abdominal wall.

The mark may be red, purple, blue, green, tan, yellow or many colors. In the 70 occurrences (in ectopic pregnancy) that we have been able to trace, the location was most often at the umbilicus, but hernial sacs and old surgical scars are frequent sites. In 2 of the collected cases and in the case described below, the discolorations appeared in still other areas. These 3 cases suggest a hypothesis for the mechanism of production of the sign.

Stabler's[5] patient, at an undeterminable time after the hemorrhage, had a sharply defined, comma-shaped, dark-purple mark, about 20 by 7 mm. in diameter, located 2 or 3 cm. downward and to the left of the umbilicus; a second, circular blue mark 2 or 3 cm. in diameter, in the midline a third of the distance from the umbilicus to the symphysis; and a third mark the color of a fresh bruise, 2 or 3 cm. in diameter, and "shaped roughly like the ace of clubs," in the skin over the left external inguinal ring. Inspection of the underlying peritoneum showed no gross abnormality: incisions into the marks themselves demonstrated ecchymoses. Stabler found no blood in the peritoneal tissues at the (unspecified) site of his incision. The amount of intraperitoneal hemorrhage was small, 90 to 120 cc.

Neumann's[6] patient, with a large but unmeasured amount of partly clotted blood in the peritoneal cavity, on the tenth day after her first symptom showed two nonumbilical ecchymoses. One was at the level, but a little to the left, of the umbilicus, and the other was 2 or 3 cm. beneath it in the midline; both were irregularly outlined; each approximated 2 cm. in diameter; one was green, and the other yellow-green.

In the third of the 3 erratic cases, the patient (F. C. 24617) had three separate ecchymoses: a small, irregular stain in the umbilicus and in one quadrant of the umbilical ring and two larger circular stains, 7 cm. in diameter, symmetrically located on either side of the umbilicus with their medial borders 6 cm. from the midline. The color approximated that of venous blood, and its hue was constant although the intensity varied. Lines of varying intensity formed arcs of concentric circles the common center of which was the umbilicus, a phenomenon that we cannot explain. The two larger spots were slightly raised; none of the three was tender.

A photograph (Fig. 1) was taken eight hours after the first symptom, which, conveniently for fixing the time of hemorrhage from the ruptured tube, was an unheralded syncope. The time of appearance of the sign is fixed as between four hours (examination by the referring physician, a competent observer) and six hours after syncope (discovery at examination on admission). The amount of blood, widely distributed throughout the peritoneal cavity and partly clotted, was 400 cc. (300 cc. measured, and 100 cc. estimated).

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The patient was thirty-seven years old, of moderate height, weighed 138 lb. and had a muscular abdominal wall with average panniculus. No hot-water bottle, electric pad, cupping or other mechanical, thermal or chemical agent that might conceivably have given rise to the ecchymoses had been used. Search of the abdominal wall from without and from within, showed no anomalies, hernias, unusual umbilical depression, apertures or thin spots. There were no adhesions. Because of the degree of shock, which was out of proportion to the moderate hemorrhage, the discolored areas were not explored.

Many theories have been suggested to explain the mechanism of the Hofstätter-Cullen sign. In a thin, translucent hernial sac, dark-colored intraperitoneal fluid can be seen through the wall: this has been demonstrated artificially by us, and clinically proved by Esau's[7] case, in which, after removal of the abdominal blood, the color in an umbilical hernia disappeared whereas that of a surrounding ecchymosis persisted. Transvisibility, however, would explain only a few of the reported cases.

Other theories advanced do not coincide with appearances that the eye records — for example, dilatation of umbilical veins or engorgement of omental vessels showing through the skin. Ordinarily, it is assumed that the color is from pigmented material that has penetrated the abdominal wall after crossing the peritoneal barrier by following adhesions or lymphatics or by finding subvisible peritoneal apertures. After crossing the peritoneum, the pigment is transported to the subcutaneous tissues by lymphatics; so, at least, goes the assumption.

There is a basis for such an assumption: networks of subcutaneous and deeper lymphatics in the abdominal wall communicate at the umbilicus with a similar network just external to the peritoneum.[8, 9] The relation between the umbilical pathway and metastasis from breast cancer has long been accented. Intra-abdominal cancer may metastasize to the umbilicus, as pointed out by Warner[10] and others.

But it is not ordinarily the function of lymphatics to pick up material, carry it a little way and then discharge it into surrounding tissues. Lymphatics carry their burden, through glands and ultimately the vascular tree, away and out of sight. Lymphatics should prevent the appearance of Cullen's sign.

Furthermore, the pigment of the sign does not follow the course of a lymphatic or group of lymphatics, as does the inflammation in lymphangitis. Contrarily, the color has the appearance of being deposited in a spot from which it spreads by direct extension. Thus in the case described above, the regular circles were at least 1 cm. in diameter smaller when seen at admission than two hours later, when the photograph was taken. Incidentally, on admission the color was a brighter, more nearly arterial red, and the small ecchymosis in the umbilicus was absent or so faint as to escape notice.

The locations of the signs in reported cases — the umbilicus, spreading outward from the umbilicus, in hernias and scars and especially the pattern of the case described, with symmetrical circles over points where vessels commonly perforate the anterior rectus sheath — suggest that, once the causative fluid has passed the peritoneum in such amounts that lymphatics do not carry it away, its distribution may be guided by fascial planes and fascial apertures, as in hypodermoclysis or extravasation of urine. There are major fascial gaps (thinning might be a better word) at the umbilicus, midline and inguinal rings and in hernias and scars; there are minor ones where vessels perforate the rectus sheath. In Stabler's case a discoloration appeared over the external inguinal ring, and both Stabler's and Neumann's patients showed marks in the midline and over possible sites of perforating vessels.

How does material cross the peritoneal barrier? Lymphatics external to the peritoneum, whether in intra-abdominal adhesions or the normal properitoneal space, would not transport material across the peritoneum but would only pick it up after crossing, and it is our impression that lymphatics do not habitually perforate the peritoneum. Scraping of holes in the peritoneum by hard lumps of feces in the colon seems far-fetched; anomalous, subvisible peritoneal apertures are reminiscent of Galen's interventricular pores. No new or special hypothesis is needed. Peritoneum is not the formaldehyde-hardened, watertight bulkhead of dissecting-room memories but a living, permeable membrane passing both fluid and particulate matter. The bulkhead concept, however, persists in the subconscious, as witnessed by the wide acceptance of endometriomas in the umbilicus or abdominal wall as an argument against the direct-implant theory of endometriosis. Yet the fluids and cells of all peritoneal exudates, to get into the peritoneal cavity from the extraperitoneal vessels whence they originate, somehow must transpass the peritoneum. Evidence of peritoneal crossing in the other direction is provided by the choking of omental lymphatics, which are extraperitoneal, by the contents of a perforated hemorrhagic cyst. Large amounts of intraperitoneal blood disappear in twenty-four hours or, if clotted, in a few days.[11] Graphite passes through the peritoneum[12]; so can a fertilized ovum — to develop in the subcutaneous tissues of the abdominal wall.[13]

Why do not colored peritoneal fluids always discolor the abdominal wall? A possible explanation is the intraperitoneal distribution of the fluid and the relative surface areas of various parts of the peritoneum. Of the total peritoneal surface available for the transpassing of material, parietal peritoneum is only a small fraction, and the peritoneum of the anterior abdominal wall is but part of the fraction. Intestine, mesentery and omentum may hold some,

much or all of a given intraperitoneal fluid away from contact with this fraction of a fraction.

Summary

The Hofstätter-Cullen sign need not be blue, can appear elsewhere than at the umbilicus and is far from pathognomonic of extrauterine pregnancy. Probably, it can be caused by any condition producing colored intra-abdominal fluid.

A variant of the sign is reported consisting of symmetrical, red, circular stains at either side of the umbilicus, over points where vessels often perforate the rectus sheath.

The location of the stains in this and in 2 somewhat similar cases, as well as the more ordinary localizations over hernias, in scars and at the umbilicus, suggests that the pigments that usually produce the phenomenon may reach their destination by following ordinary fascial planes and openings rather than by depending upon exceptional lymphatic function or subvisible peritoneal apertures.

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THE EFFECT OF ORAL THERAPY WITH COBALTOUS CHLORIDE ON THE BLOOD OF PATIENTS SUFFERING WITH CHRONIC SUPPURATIVE INFECTION*

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DURING a study of prolonged suppurative infection in 91 young men, we observed reticulocytosis, which was followed by increases in hematocrit and hemoglobin values, in the blood of patients being given cobaltous chloride by mouth.[1] These findings were not completely unexpected since it has long been known that cobalt is a hematopoietic agent effective in deficient[2] and healthy animals.[3] Therapy with cobalt apparently stimulates red-cell production in children,[4] as well as in adults,[5] and also protects animals from developing anemia when sterile suppuration is induced experimentally.[6]

As far as we are aware cobalt has not been employed in this country in the treatment of patients ill with chronic sepsis. This report therefore presents observations on the blood of 9 patients suffering with prolonged suppurative infections who were treated for two to eleven weeks by the daily oral administration of 20 to 60 mg. of cobaltous chloride.

Material and Methods

Methods

Hemoglobin determinations were made by a photoelectric method[7]; hematocrit values, red-cell counts, white-cell counts, reticulocyte counts and differential white-cell counts were done according to methods described by Wintrobe.[8] Plasma volume was determined by Gregersen's[9] modification of the technic of Gibson and Evans,[10] using the dye T-1824, plasma iron, after that of Kitzes et al.,[11] and plasma copper by a modification of the method of Cartwright and his associates.[12]

Patients

Nine male patients were selected for study. Their average age was twenty-five years (the oldest was thirty-six and the youngest eighteen years of age). Three patients had been injured by automobiles, and 6 had been wounded by bullets or fragments from land mines. When first selected for this study patients had already spent an average of twenty-eight months in hospitals because of chronic osteo-

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myelitis or chronic soft-tissue suppuration. At the time of injury and thereafter all patients had received adequate therapy with blood and blood substitutes and, in addition, had been treated with sulfonamide derivatives (usually sulfadiazine), penicillin and streptomycin. Reconstructive surgical procedures had been carried out on numerous occasions in all patients.

When first observed by us all patients showed evidence of chronic sepsis as judged by drainage of pus from wounds, pyuria, continued fever or radiographic evidence of bone sequestra. There was no clinical evidence of vitamin or protein deficiencies although all patients had lost weight. The red-cell sedimentation rate was increased, and in all cases cultures of organisms were obtained from sites of sepsis.[1] The organisms were identified and were usually found to be resistant to penicillin or streptomycin. In these patients plasma iron levels were low, and plasma copper levels were increased. Control measurements of blood volumes, hemoglobin levels, hematocrit values and cell counts were made on at least two occasions before therapy was instituted.

After the patients had been observed during the control period they were treated with 20 to 60 mg. of cobaltous chloride in tablet form taken orally each day after meals. Treatment was continued for eleven weeks in 4 cases, for four weeks in a second group of 4 patients, and for two weeks in 1 patient. During this time none of the patients received transfusions or therapy with other hematopoietic agents.

Two patients (Cases 3 and 4, Table 1), whose wounds were infected with penicillin-fast organisms, had previously been given injections of penicillin on numerous occasions without clinical effect, and were again treated with penicillin while taking cobalt. The penicillin was administered at a time when reticulocyte response had already been observed and, in our opinion, did not affect the course of the illness.

TABLE 1. *Initial and Final Levels of Red-Cell Counts, Hemoglobin, Hematocrit and Total Circulating Hemoglobin in 9 Patients with Chronic Suppuration Treated with Cobaltous Chloride.*

Case No.	Duration of Cobalt Therapy	Dosage of Cobalt	Measurement	Red-Cell Count	Hemoglobin	Hematocrit	Total Circulating Hemoglobin
	wk.	*mg./day*		*x10⁶*	*gm./100 cc.*	*%*	*gm.*
1	11	20	Initial	4.35	13.8	44.8	610
			Final	5.75	16.0	52.0	850
2	11	20	Initial	4.82	14.5	43.8	640
			Final	6.58	15.7	51.0	860
3	11	20	Initial	4.90	13.3	44.2	660
			At 8 weeks	5.35	14.9	46.5	762
			Final	4.68	12.5	41.0	650
4	11	20	Initial	5.10	13.5	41.7	650
			Final	6.10	15.3	50.0	880
5	7	60	Initial	4.66	13.6	41.3	550
			Final	5.50	14.5	48.0	780
6	2	60	Initial	5.10	14.0	45.5	810
			Final	6.30	15.7	51.0	990
7	4	60	Initial	4.48	12.3	38.0	670
			Final	5.38	15.8	53.0	1100
8	4	60	Initial	4.69	14.8	45.2	670
			Final	5.52	16.2	52.0	950
9	4	60	Initial	3.42	11.0	30.8	470
			Final	5.19	13.5	41.0	670

TABLE 2. *Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients with Chronic Suppurative Infection.*

Group	Red-Cell Count	Hemoglobin	White-Cell Count	Neutrophils	Lymphocytes	Basophils
	x10⁶	*gm./100 cc.*	*x10³*	*%*	*%*	*%*
Bed-ridden controls without infection (10 patients)*	5.5	15.7	8.1	60.5	33	0.5
Patients with infection before therapy (9 patients)	4.6	13.4	8.8	56.0	38	1.0
Patients with infection after therapy (9 patients)	5.7	15.1	9.3	55.0	39	0.5

*Reported in earlier study.[1]
†Figures for 4 patients only.

Results

Hematologic data on individual patients are given in Table 1 and Figure 1. Average data for the 9 patients during the control period and at the end of therapy with cobaltous chloride are recorded in Table 2 and are contrasted with average data obtained from 10 patients bed ridden with fractures or orthopedic abnormalities, who were free from infection during their illness.[1]

Before treatment, red-cell counts, reticulocyte counts, hemoglobin concentrations, hematocrit levels and total circulating hemoglobin were constant and reduced below the levels found in the bedridden control subjects. The significant deviations curred during the first eight weeks of treatment with cobalt. An extensive sequestrectomy of the femur was performed during the ninth week of therapy, and, during the next two weeks while he was still taking cobalt, the total circulating

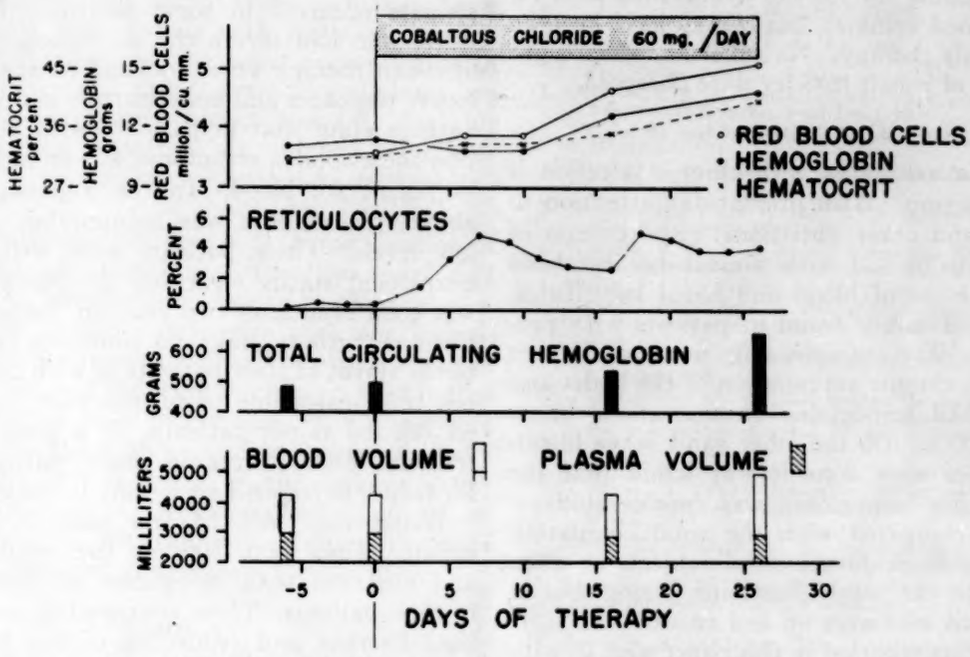

FIGURE 1. *Effect of Therapy with Cobaltous Chloride on the Blood of a Nineteen-Year-Old Male Patient with Chronic Cystitis and Osteomyelitis Following a Bullet Wound.*

from the normal were in measurements of total circulating hemoglobin, which was reduced on the average 26 per cent below levels found in the controls.

After treatment with cobaltous chloride reticulocyte responses were observed in each of the 9 patients. These occurred as early as the fourth day and continued throughout therapy. The maximal reticulocyte percentages were usually observed between the sixth and tenth days, and did not exceed 5 per cent in any case. A typical reticulocyte response is shown in Figure 1. In this patient, as in the other 8 (Table 1), a steady increase in red-cell counts, hematocrit levels and total circulating hemoglobin followed the reticulocyte response. In Case 3 considerable increases in blood values occurred during the first eight weeks of treatment with cobalt. An extensive sequestrectomy of the femur was performed during the ninth week of therapy, and, during the next two weeks while he was still taking cobalt, the total circulating hemoglobin, red-cell count and hematocrit levels returned to pretherapy levels.

From Table 2 it can be seen that on the average the blood values of the 9 patients had reached normal levels after cobalt therapy. There was a significant change in the blood volume, owing in the main to a 30 per cent increase in the circulating red-cell mass, the plasma volume changing but slightly. The total circulating hemoglobin increased, on the average, 29 per cent above the levels before therapy. White-cell counts and differential cell counts showed few changes and mean corpuscular volume altered but slightly. In 4 patients, in whom measurements were made before and after treatment with cobalt, plasma iron and copper levels were not affected by cobalt therapy.

TABLE 2 (*Continued*).

Eosinophils	Monocytes	Hematocrit	Mean Corpuscular Volume	Blood Volume	Plasma Volume	Total Circulating Hemoglobin	Plasma Iron	Plasma Copper
%	%	%	*cu. microns*	*cc.*	*cc.*	*gm.*	*microgm./100 cc.*	*microgm./100 cc.*
2.0	4.0	47.2	86	5060	2660	790	120	95
2.5	2.5	41.7	90	4830	2670	648	83†	144†
2.5	3.0	49.1	86	5470	2910	872	83†	136†

Toxicity

During therapy with cobalt slight loss of appetite was observed in 2 patients. All patients developed a dusky discoloration of the skin, especially marked below the eyelids. This change in the color of the skin was probably due to the dye T-1824 used for measuring blood volumes, but it may have been an effect of cobalt therapy. No other abnormal signs or symptoms of cobalt toxicity were observed.

Discussion

The anemia associated with chronic infection is usually not severe. With present-day attention to the protein and other nutritional requirements of the chronically ill and with present-day emphasis on the liberal use of blood and blood substitutes, gross anemia is rarely found in patients with prolonged sepsis. For example, only 6 out of 91 men suffering with chronic suppuration of the bones and soft tissues had hemoglobin concentrations below 12 gm. per 100 cc. On the other hand, when blood-volume studies were done it was found that the total circulating hemoglobin was considerably reduced when compared with the total circulating hemoglobin of bed-ridden control subjects or when compared with the total circulating hemoglobin of healthy persons who were up and about.[1]

The 9 patients reported in this paper were ill with chronic sepsis. In them plasma copper was elevated and plasma iron was reduced. Although hemoglobin concentrations and red-cell counts were reduced only slightly below levels found in the control subjects, the total circulating hemoglobin was reduced on the average by 26 per cent and may therefore have indicated lowered total blood volume.

Hematopoietic responses to therapy with cobaltous chloride, which were observed in each patient, indicate that cobaltous chloride produced an active stimulus to erythropoiesis, since a distinct reticulocytosis preceded the rise in erythrocyte count. Reticulocytes are not increased and do not increase spontaneously in patients at times when they are ill with chronic sepsis. The reticulocytes in the 91 patients mentioned above averaged 0.7 per hundred red blood cells and in only 1 case did they reach 2.0 per cent. Spontaneous increases in blood values were never observed when suppuration persisted. This, of course, is common knowledge.[8, 13]

Preliminary observations on the effect of cobalt on the blood of normal and anemic persons have been reported in the German literature by Weissbecker and Maurer.[5] They state that after daily oral therapy with 500 mg. of cobalt chloride a reticulocyte peak occurred on the third day, and thereafter increases in erythrocyte, hemoglobin and hematocrit values occurred. Mean corpuscular volume and red-cell diameter decreased. The Price–Jones curve shifted to the left, and its base broadened. Osmotic resistance, serum bilirubin, white-cell count and differential cell count remained unchanged. Blood volume increased, but plasma volume remained steady. In normal adults a "true" polycythemia developed, and blood levels returned to normal in patients anemic from blood loss.

In the anemia of chronic infection adequate responses occurred in some patients. However, in those who had severe chronic infection the effects of cobalt therapy were small and consisted of reticulocyte responses and bone-marrow maturation. The authors state that in patients with chronic infection the available serum iron was an index of ability to regenerate blood. In the 9 patients reported above, plasma iron was reduced but not to very low levels. These patients were well fed. Their nutritional status regarding protein and vitamins was good even after two years in the hospital. The German authors make no comment on the nutritional status of their patients ill with chronic sepsis, but it is reasonable to suspect that they were not so well fed as our patients. It is possible that nutritional disturbances in some patients account for failure to respond maximally to cobalt.

Weissbecker and Maurer used large doses of cobalt. They gave 500 mg. by mouth each day and observed toxic symptoms in themselves and in their patients. These consisted of nausea, vomiting, diarrhea and reddening of the face and extremities, which was accompanied by hot flushes. With 60 mg. a day by mouth after meals neither ourselves nor our patients experienced untoward symptoms. However, 2 of the patients suffered somewhat from anorexia.

The mode of action of cobalt on the blood remains a mystery. Specific effects of cobalt therapy on anemia are seen in cattle and sheep that graze on grass deficient in this trace element,[2] and good hematopoietic responses occur after therapy with very small amounts (0.1 mg.) of cobalt. Castle,[14] in a recent talk, suggested that cobalt-deficient animals are really suffering from vitamin B_{12} deficiency. He speculated that normally bacteria in the rumen of cattle synthesize vitamin B_{12} — a cobalt-containing organic substance — and that the vitamin exerts a specific effect on hematopoiesis after it is absorbed. He also suggested that when the animals live on cobalt-deficient feed the intestinal flora are not able to form the vitamin. Consequently, the animals develop vitamin B_{12} deficiency and become anemic.

It does not seem possible that cobalt exerts a specific effect on the blood in patients with chronic infections. Their anemia is refractory to therapy with liver, which contains vitamin B_{12}, and they require relatively large quantities of cobalt for erythropoiesis to take place. It is more likely that the hematopoiesis that follows massive cobalt therapy is due to a nonspecific stimulus to the bone marrow. This may be a consequence of generalized tissue anoxia or may follow impaired oxygen trans-

fer from the blood to the bone marrow. There is good evidence in the literature that cobalt inhibits the respiration of micro-organisms as well as animal tissues and tumors[15] and that it does so by inhibiting –SH groups of enzyme systems.[16] Oral therapy with sulfur-containing amino acids, such as cysteine and also to a lesser extent with histidine, inhibits the effects of cobalt in producing polycythemia in rats, and parenteral cobalt-cysteine complexes are also unable to produce polycythemia.[17] Ascorbic acid, a reducing substance, also inhibits the effects of cobalt in producing polycythemia in rabbits[18] and dogs.[19]

As our patients developed a blue discoloration of the skin we speculated that the "cyanosis" and bone-marrow anoxia were due to methemoglobin, produced by cobalt interference with the normal reconversion in the red blood cell of methemoglobin to hemoglobin — a reducing mechanism that is continuously taking place in the blood.[20] We therefore examined the blood of 4 patients spectroscopically but were not able to detect methemoglobin after therapy with cobalt. The mechanism of cobalt activity in patients with chronic infection therefore remains unexplained and requires further study.

Summary

Nine patients suffering with chronic suppurative infections were treated with 20 to 60 mg. a day of cobaltous chloride given by mouth for a period of two to eleven weeks. In all patients a reticulocytosis was observed within six days. This was followed by increases in red-cell counts, in hemoglobin values, in hematocrit levels, in blood volume and in total circulating hemoglobin.

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ERYTHROPOIETIC EFFECT OF COBALT IN PATIENTS WITH OR WITHOUT ANEMIA*

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COBALT in the form of one of its salts, usually cobaltous chloride or cobaltous nitrate, has been shown to produce polycythemia in amphibia, birds and mammals.[1-3] In mammals the increased concentration of red blood cells in the circulation is due, as in other types of polycythemia, largely to an increase in the circulating red-cell mass.[4, 5] That the polycythemia is produced by increased red-cell production is indicated by an initial or by a maintained reticulocytosis,[6, 7] and an increase in erythroid cells in the bone marrow[8, 9] and in extramedullary locations.[9] In some species the slight bilirubinemia[7] presumably results from a partially compensatory increase in erythrocyte destruction. There is no evidence that cobalt administration causes the development of red blood cells containing an abnormal form of hemoglobin[10] or one with a lessened capacity for the transport of oxygen.[9] However, the resemblances of cobalt polycythemia to experimental polycythemia induced in various ways by anoxia of the bone-marrow cells may find an explanation in recent observations[11, 12] indicating that cobalt inhibits the respiration of certain bacteria, perhaps owing to the formation of partially reversible complexes between cysteine or histidine, cobalt and oxygen. Results in animal experiments suggest that such complexes are not readily dissociated in the body[10] and so point to the possibility that their formation creates in effect anoxia of the erythroid cells of the bone marrow, with its characteristic increase in erythropoiesis.

Since the pioneer observations of the Waltners[1] in 1929, metallic cobalt or its salts have been administered in animals and in man in efforts to combat the anemia produced by disease. For example, Kleinberg, Gordon and Charipper[8] reported that cobaltous nitrate was able to counteract the inhibitory effect on erythropoiesis of benzol administration in rabbits. Recently Wintrobe and his associates[13] showed that cobalt administration abolished the anemia or even produced polycythemia in rats in which sterile inflammation had been created by the intramuscular injection of turpentine. Only a few results, for the most part all too briefly documented, have been reported from the use of cobalt salts as a stimulus to erythropoiesis in human disease.[14-18] However, almost at the time of the beginning of the present investigation, Weissbecker and Maurer[19] briefly indicated in the German literature that the oral administration of 500 mg. of cobaltous chloride daily produced with regularity in normal subjects reticulocyte responses and thereafter increases in red-cell, hemoglobin and hematocrit values. They confirmed the animal observations showing a decrease in mean corpuscular volume and diameter of the red blood cells and noted, likewise, an increase in circulating red-cell mass but not in plasma volume. No changes in serum bilirubin or in total or differential white-cell counts were observed. In some patients with the anemia of chronic infection, similar or less pronounced erythropoietic responses occurred. The toxic effects observed consisted of anorexia, nausea, vomiting, diarrhea and flushing of the face and extremities.

In the present work, an attempt was made to study the erythropoietic effect of cobalt first in hematologically normal patients. Then, especially because of the apparently successful results of Kleinberg and his associates[8] in rabbits poisoned with benzol, it was proposed to extend the observations to patients with anemias refractory to recognized forms of treatment. If effective in causing increased erythropoiesis, cobalt therapy might be useful as a substitute, at least in part, for the repeated transfusions required in the treatment of such patients.

METHODS

Cobaltous chloride ($COCl_2.6\ H_2O$) in the form of a 2.5 per cent aqueous solution was administered to 61 patients. Unless otherwise indicated, the dose of the solution employed was 4 cc. containing 100 mg. of cobaltous chloride given orally, thrice daily after meals, well diluted with water.

During a control period of not less than five days, two or more complete blood counts and daily reticulocyte counts were made. Then, with the institution of cobalt therapy, daily reticulocyte counts were continued for at least ten days in most patients, and complete blood counts were made at least once weekly for two to fourteen weeks. The red-cell and white-cell counts were made from venous blood samples in the usual manner with the use of United States Bureau of Standards certified pipettes. Hemoglobin estimations were done with an Evelyn photoelectric colorimeter with a factor of 2.58. It was considered that 15.6 gm. of hemo-

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globin was equivalent to 100 per cent. Hematocrit determinations were performed by the method of Wintrobe, and the mean corpuscular volume and mean corpuscular hemoglobin concentration were calculated. Reticulocytes were counted by means of coverslips previously coated with a film of brilliant cresyl blue dissolved in absolute alcohol. After the film was dry, a fresh drop of blood was spread upon the coverslip in the usual manner and was thereafter fixed and counterstained with Wright's stain. The percentage of reticulocytes was then estimated by a count of at least 1000 red blood cells under the oil immersion lens.

TABLE 1. *Types of Patients Treated and Number Showing Increased Erythropoiesis or Toxic Effects from the Oral Administration of Cobaltous Chloride.*

DIAGNOSIS	TOTAL PATIENTS TREATED	PATIENTS TREATED FOUR WEEKS OR MORE	NO. SHOWING ERYTHROPOIETIC EFFECTS		TOXIC EFFECTS	NO. OF PATIENTS AFFECTED
			ON RETICULOCYTES	ON HEMOGLOBIN		
A. Patients without anemia:						
Convalescents	17	10	17	10	Severe anorexia (1 patient), nausea and vomiting (1 patient) while on 1200 mg. daily	2
Pernicious anemia in remission	12	0	—	—	Nausea and vomiting (12 patients); other symptoms described in text.	12
Totals	29	10	17	10		14
B. Patients with anemia:						
Chronic infections	5	4	2	2	Anorexia (2 patients), nausea and vomiting (2 patients), occasional vomiting (1 patient)	4
Refractory anemia	5	4	0	0	Nausea and vomiting (3 patients)	3
Leukemia and lymphoma	16	10	—	3	Anorexia (1 patient), nausea and vomiting (6 patients), occasional vomiting (4 patients), substernal pain (3 patients), dizziness (1 patient)	11
Chronic nephritis	2	0	0	—	Nausea and vomiting (2 patients)	2
Hypochromic anemia	2	0	1	1	Anorexia (2 patients)	2
Cooley's trait	1	1	1	1	Nausea and vomiting after 9 weeks (1 patient)	1
Hepatic cirrhosis	1	1	0	0	None	0
Totals	32	20	4	7		23
Grand totals	61	30	21	17		37

RESULTS

The types of patients to whom cobaltous chloride was administered are indicated in Table 1. In the 31 patients who were treated for less than four weeks, cobalt administration was discontinued in 24, chiefly because of the irritant effects on the alimentary tract noted in Table 1, and in 7 convalescent subjects because early discharge from the hospital rendered further observations impossible. The erythropoietic effects observed in the patients without anemia are summarized in Table 2, and illustrations of those noted in 1 normal and in 3 anemic patients are presented in Figures 1 to 4.

Patients without Anemia

These 17 patients were without significant hematologic abnormality and can be subdivided into three groups chiefly on the basis of the amount of cobaltous chloride administered.

Subgroup A. Eight patients with various psychoses were given 100 mg. of the medication in a single daily dose for six days. During this period, as shown in Table 2, small reticulocyte responses were observed in 6 patients. The dose of cobalt was then increased to 200 mg., once daily. The 2 remaining patients then showed within seven days reticulocyte responses for the first time, and the other 6 patients showed a second and slightly greater peak of reticulocytes. Thereafter, therapy with cobaltous chloride was continued with occasional unavoidable omissions, especially after the ninth week, for twelve weeks in all. During this time, moderate increases in red blood cells, in hemoglobin and in hematocrit of venous blood samples occurred in all but 1 case (Case 7, red blood cells), as shown in Table 2. No toxic effects were noted in any of the patients of this group, nor did any significant improvement in mental status develop.

Subgroup B. Seven patients — in 4 cases convalescent from cerebral vascular accidents and in 1 each with prostatism, mental deficiency and senility — were given cobaltous chloride in a dose of 100 mg. three times a day. In 6 patients the drug was administered for only one or two weeks prior to discharge from the hospital. However, daily counts showed within ten days reticulocyte peaks in most cases significantly greater than those in the cases included in Subgroup A. In the remaining patient

(Case 9), a sixty-seven-year-old man with marked generalized osteoporosis and osteoarthritis, the drug was administered for eleven weeks. The striking results upon red-cell and hemoglobin levels are of a pre-existing and otherwise silent duodenal ulcer, no unfavorable effects attributable to the medication were noted in the patients comprising this subgroup.

TABLE 2. *Erythropoietic Effects of Cobaltous Chloride Administration in Patients without Anemia.*

CASE NO.	RED-CELL COUNT		HEMOGLOBIN		HEMATOCRIT		RETICULOCYTES					DURATION OF THERAPY
	INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL	CONTROL	PEAK 1		PEAK 2		
	$\times 10^6$	$\times 10^6$	%	%	%	%	%	%	day	%	day	wk.
Subgroup A (100 mg. daily for six days, followed by 200 mg. daily):												
1	4.14	4.58	71	83	35	41	0.8	2.8	5	3.7	15	12
2	4.74	6.26	89	105	43	52	0.4	2.1	7	3.1	14	12
3	4.65	5.63	85	108	41	51	0.6	—	—	1.4	14	12
4	4.75	5.70	90	100	43	49	0.8	1.9	6	2.2	12	12
5	4.36	5.23	83	106	40	49	0.8	1.2	4	3.1	12	12
6	4.03	4.88	80	93	37	43	0.8	1.5	4	2.5	15	12
7	5.29	5.18	87	109	43	47	0.8	—	—	2.2	14	12
8	4.63	6.99	88	103	41	51	0.4	2.0	5	2.8	13	12
Subgroup B (300 mg. daily):												
9	3.92	6.93	81	116	38	59	0.9	3.0	6	—	—	11
10	4.70	4.67	92	91	47	43	0.7	4.1	10	—	—	2
11	5.01	5.41	85	92	41	44	1.4	5.3	7	—	—	2
12	4.04	3.82	75	66	37	36	0.8	6.1	6	—	—	2
13	4.25	—	81	—	37	—	2.2	5.1	4	—	—	2
14	4.37	—	80	—	43	—	1.9	8.3	6	—	—	1
15	4.71	4.95	91	92	45	45	0.9	2.3	9	—	—	2
Subgroup C (300 mg. the first, 600 mg. the second, 900 mg. the third day and thereafter 1200 mg. daily):												
16	4.41	5.30	83	98	42	52	0.5	1.6	7	—	—	6
17	4.41	4.88	87	96	42	49	0.8	1.6	6	—	—	2

summarized in Table 2 and are shown graphically in Figure 1. Although blood loss during the first week of treatment may have been responsible for the first reticulocyte peak, thereafter somewhat elevated reticulocyte counts appeared in successive waves of several days each. After ten weeks of treatment, the patient began to complain of poor appetite and sensations of fullness in the head. Consequently, cobalt administration was stopped a week later, and five days thereafter, at the height of the polycythemia, 500 cc. of blood was removed

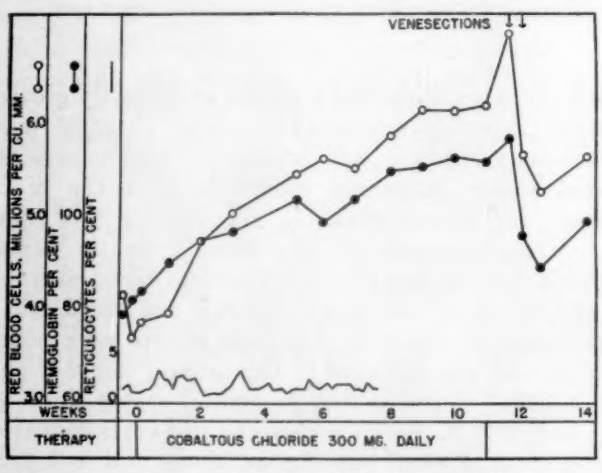

FIGURE 1. *Results of Cobalt Administration in Case 9. This was a sixty-seven-year-old man with generalized osteoporosis and osteoarthritis. Because of manifest polycythemia after eleven weeks of cobalt therapy, two venesections of 500 cc. each were performed. The red blood cells so obtained contained no abnormal forms of hemoglobin and survived normally in a suitable recipient.*

on two successive days. Except for the hematemesis in this patient, which presumably, in the light of a subsequent x-ray examination, was due to irritation

Subgroup C. Two patients (Cases 16 and 17), who were convalescent from cerebral vascular accidents, received cobaltous chloride as follows: on the first day 100, on the second day 200, on the third day 300, and thereafter 400 mg. three times daily. Both patients showed reticulocyte responses

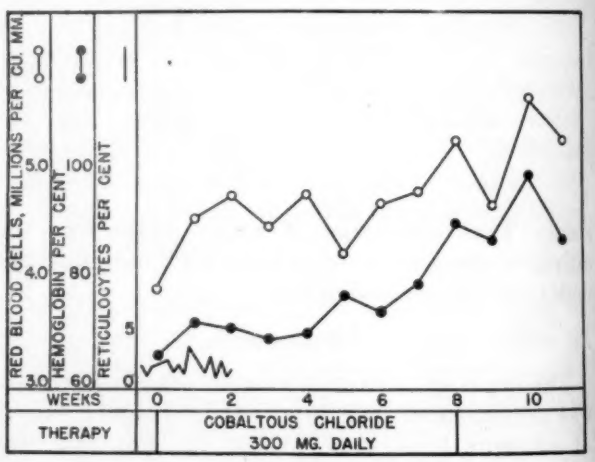

FIGURE 2. *Results of Cobalt Therapy in a Fifty-Three-Year-Old Man (Case 18) with Mild Hypochromic Anemia due to Chronic, Moderately Active Rheumatoid Arthritis.*

of slight degree. After two weeks of this regime, 1 patient (Case 17) demonstrated severe nausea and vomiting with hemoconcentration that disappeared when the drug was stopped. The other patient (Case 16) was successfully treated for six weeks. Daily reticulocyte counts were performed throughout this period and showed a wave-like rise and fall over periods of several days. During this time, the red blood cells, hemoglobin and hematocrit exhibited the moderate increase shown in Table 2.

The patient complained only of anorexia and had no nausea or vomiting.

An attempt was made to administer 100 mg. of cobaltous chloride, three times a day, simultaneously to two groups of 6 patients with pernicious anemia maintained in complete remission in an outpatient clinic by means of monthly injections of concentrated liver extract. However, without exception each patient reported a week later that with the first dose of the medication symptoms appeared. Indeed, after either the first dose or the first few doses, nausea and vomiting, sometimes of considerable severity, compelled the discontinuation of the medication by the patient himself. Subsequent inquiry revealed that 2 patients had also noticed palpitation and 2 had experienced constipation (Table 1). In individual patients nosebleed, swelling of the hands and feet, abdominal pain, dizziness and diarrhea appeared clearly to result from the medication. All symptoms disappeared a few hours after the drug was stopped.

Patients with Anemia

Cobaltous chloride was administered at the rate of 100 mg., three times a day, to 32 patients with various types of anemia refractory to treatment. Of these, 20 took the medication for over four weeks. The number of each type of patient treated, as well as the untoward symptoms that occurred, is shown in Table 1. Of the 5 patients with moderate anemia associated with chronic infections (pulmonary tuberculosis in 3 and rheumatoid arthritis in 2), 4 received treatment for over four weeks; of these, 2 patients (Cases 18 and 19) showed reticulocyte responses and subsequent rises in blood values. Case 18 was a fifty-three-year-old mason with chronic rheumatoid arthritis, who ran a temperature above 100°F. and an elevated sedimentation rate during the period of cobalt administration. Case 19 was a forty-eight-year-old pipe fitter, who showed multilocular cavitation of the upper right lung and nodular lesions in the centers of both lungs. On bed rest during the period of cobalt administration he ran a low-grade fever, and occasional sputums were positive for tubercle bacilli without evidence of change in x-ray films of the chest. Cobalt administration appeared to aggravate mildly this patient's occasional episodes of nausea and vomiting. The hematologic data for these patients are presented in Figures 2 and 3. Five patients with "refractory" anemia and hypercellular bone marrow, presumably of the type described by Bomford and Rhoads,[20] of whom 4 were treated for over four weeks with cobaltous chloride, yielded no definite reticulocyte responses or rises in blood values.

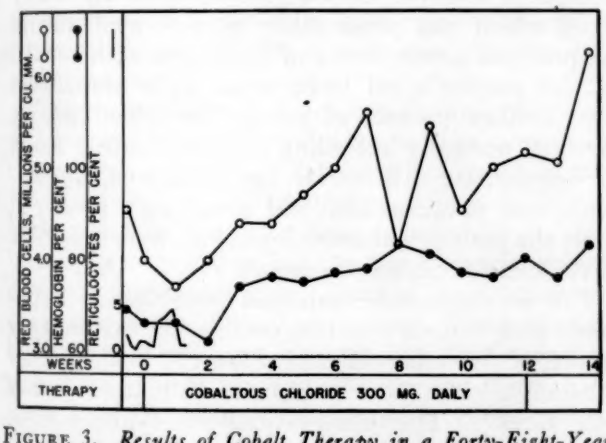

FIGURE 3. *Results of Cobalt Therapy in a Forty-Eight-Year-Old Man (Case 19) with Mild Hypochromic Anemia due to Chronic, Advanced Pulmonary Tuberculosis.*

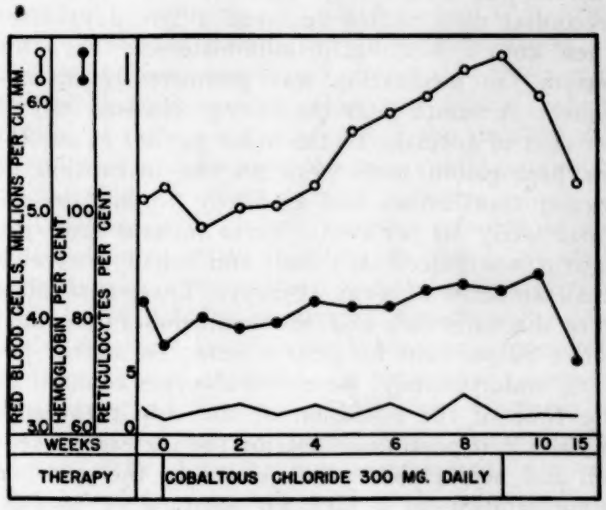

FIGURE 4. *Results of Cobalt Therapy in a Thirty-Seven-Year-Old Italian Woman (Case 22) with Familial Microcytic (Cooley's Trait) Anemia.*

Note the relatively greater increase in the red blood cells than in the hemoglobin in response to cobalt administration.

Sixteen patients with anemia accompanying various forms of leukemia or lymphoma were treated with cobaltous chloride. Of these, 10 received the material for over four weeks. In 2, daily reticulocyte counts were made during the first ten days of therapy and showed no evidence of significant increase. In 2 other patients, both with anemia associated with reticulum-cell sarcoma, there was perhaps suggestive evidence of an effect upon circulating red-cell values that became apparent more than a month after cobalt treatment had been begun. Thus, in 1 patient (Case 20) during a period of four months, nitrogen mustard therapy on three occasions and multiple transfusions within a few days of 2500 or more cc. of whole blood on four occasions failed to elevate the hemoglobin more than temporarily above 54 per cent. However, after cobalt therapy for two months, a fifth series of transfusions comprising 2500 cc. of whole blood raised the hemoglobin promptly from 32 to 83 per cent. Cobalt therapy was then continued for two more months, during which the hemoglobin values remained above 85 per cent. Two months after the cessation of cobalt therapy, the hemoglobin was 72 per cent. At this time, because of enlargement

of lymph nodes, a course of nitrogen mustard therapy was given. A month later the patient's hemoglobin was 57 per cent, and he was again started on therapy with cobaltous chloride. Two weeks thereafter, when his hemoglobin was 39 per cent, he was given multiple transfusions comprising 3500 cc. of whole blood, which brought his hemoglobin up to 73 per cent. During the next six weeks, cobalt therapy was continued, and the hemoglobin increased to 99 per cent. At that time cobalt therapy was stopped temporarily because of an episode of precordial pain, which recurred a few days later when cobalt was again administered. For this reason, the medication was permanently discontinued. A month later the hemoglobin was still 83 per cent of normal. In the other patient (Case 21) the hemoglobin level prior to the institution of regular transfusions had gradually declined to approximately 50 per cent. Three months later the patient was placed on cobalt and began to receive small amounts of x-ray therapy. The transfusions were discontinued, and the hemoglobin remained above 80 per cent for over a year. In neither patient, unfortunately, were reticulocytes counted at the time of the initiation of the cobalt therapy. In each it is possible to ascribe the increase in red-cell and hemoglobin values either to the previous administration of a nitrogen mustard or to concomitant, though seemingly insufficient, irradiation therapy.

A third patient (Case 22), with chronic lymphatic leukemia, was given two courses of radioactive phosphorus one month and one week respectively before he was placed on 200 mg. of cobaltous chloride daily. Cobalt administration was continued for five weeks, during which the elevated white-cell count fell gradually to normal and the hemoglobin increased from 39 to 58 per cent. The dose of cobalt was then reduced to 100 mg. daily and was continued for another five weeks, when the hemoglobin had reached 94 per cent. Without further cobalt administration the hemoglobin slowly declined in the next eight months to 74 per cent, and the white-cell count gradually rose to about 80,000. Again, the interpretation of the dramatic hemoglobin response is complicated by the previous administration of radioactive phosphorus.

Two patients with the anemia of chronic nephritis could not tolerate the drug for more than a few days and exhibited no reticulocyte responses. Of 2 patients with hypochromic (iron-deficiency) anemia, 1 showed a definite reticulocyte response and rise in red cells and hemoglobin despite the presence of inoperable carcinoma of the stomach. A clear-cut erythropoietic response to cobaltous chloride therapy was obtained in 1 patient (Case 23), a thirty-seven-year-old Italian housewife, with familial microcytic (Cooley's trait) anemia. The pertinent hematologic data are presented in Figure 4. Moderate nausea and vomiting appeared after nine weeks of therapy and persisted for six days until the medication was discontinued. A patient with moderate anemia due to cirrhosis of the liver was given cobaltous chloride for more than four weeks without detectable effect on reticulocyte or other blood values.

Discussion

On the basis of these observations, it seems clear that cobaltous chloride when administered in man in sufficient doses causes with some regularity increased erythropoiesis in hematologically normal subjects. The reticulocyte responses occurred within ten days of the institution of cobalt therapy, and so resemble in their chronology those resulting from hemorrhage, anoxia or iron or liver-extract administration under circumstances appropriate to each. This is seemingly consistent with the possibility, referred to above, that cobalt interferes with the transport of oxygen in the erythroid cells of the bone marrow because of its ability to form oxygen-binding complexes with certain amino acids such as cysteine and histidine. If so, the agent would be expected to be effective in elevating the hemoglobin level in patients with little or no anemia rather than in those with severe anemia, in whom a powerful anoxic stimulus to erythropoiesis presumably already exists.

Like Orten and Bucciero[10] in their animal experiments, we were unable to demonstrate any abnormalities in the light-transmission curve of oxyhemoglobin using the Beckman spectrophotometer. The pigment was derived from circulating red blood cells removed from a patient (Case 9), nearly all of which had presumably been formed during the previous eleven weeks of treatment with cobalt. As this patient's red blood cells, when transfused into another patient of compatible blood group, survived normally according to identification made by appropriate differential agglutinations, no evidence was obtained that red blood cells produced while the patient was receiving cobalt were defective as vehicles for oxygen transport.

The erythropoietic responses observed in 2 patients with chronic infection confirm the preliminary report of Weissbecker and Maurer[19] and further substantiate the observations of Robinson, James and Kark.[21] The observations of Waltner,[14] of Baxter[18] and possibly of Kato[16] suggest an effect of cobalt in "secondary," presumably hypochromic anemias in children due to iron deficiency with or without infection. In our experience also cobalt was efficient in raising the blood values of 1 of 2 patients with hypochromic anemia due, presumably, to blood loss from an inoperable cancer of the stomach. Iron, however, would be the therapeutic agent of choice in such a patient unless it was rendered ineffective because the cancer was exerting a "toxic" inhibition on erythropoiesis resembling that perhaps existing in chronic infection.[13] The

definitive erythropoietic response in 1 patient with familial microcytic (Cooley's trait) anemia indicates a possible use for cobalt therapy in a condition that is completely refractory to iron and other substitution treatment.

Because it was the main objective of the study, it was disappointing to find that cobalt was completely ineffective in raising the hemoglobin level in 5 patients with "refractory" anemia of idiopathic origin associated with hypercellular bone marrow.[20] The coincidental use of other forms of treatment rendered the results merely suggestive in the 2 patients with anemia associated with reticulum-cell sarcoma and in 1 with chronic lymphatic leukemia. No certain benefit was remarked in any of the other patients with leukemia or lymphoma. In the anemias of chronic nephritis and cirrhosis, our studies, though negative, are perhaps too few to permit conclusions.

The toxicity of cobalt at dosage levels capable of causing polycythemia is difficult to estimate from reports in the literature. When administered orally, cobalt salts are largely excreted in the feces, and even the portion absorbed from the intestinal tract is mostly lost in the urine within a few days.[22,23] Thus, at the height of the polycythemia produced in rats, only 40 to 50 microgm. of cobalt may be found in the entire body of the animal.[24] When cobalt salts are injected, elimination is largely in the urine and bile,[23, 25] but as much as 5 per cent may be retained by the tissues ten days later.[23] Presumably as a result of the poor absorption of the cobalt salts, the production of significant polycythemia in the adult rat requires the daily oral administration of about 40 mg. per kilogram of body weight, in contrast to only 2.5 mg. of cobaltous chloride daily by injection.[26]

Early observations in animals showed that when given orally in sufficient dosage to dogs cobalt salts caused irritation of the intestine and death in convulsions. Ten milligrams killed a frog in half an hour, and 300 mg. was fatal to a rabbit in three hours. In dogs 200 to 300 mg. per kilogram of body weight caused vomiting, diarrhea and sometimes acute nephritis. With larger doses, dyspnea and a fall of blood pressure appear, and death may result from cardiac paralysis.[27] On the other hand until a certain daily oral dosage level is reached, which varies in different species and individuals, there may be no signs of toxicity and then only a poor appetite, which promptly improves with the discontinuance of the cobalt.[28] In the opinion of LeGoff,[29] who has studied the subject of cobalt toxicity both in animals and in man, cobalt is not more dangerous than iron, the immediate toxic actions of which it seems to imitate. The subcutaneous injection of 10 to 50 mg. of cobaltous chloride in human subjects caused a sensation of heat in the face and a fall of blood pressure. To one patient LeGoff gave 90 mg. daily orally for a hundred days, and to another 122 subcutaneous injections of 25 mg. each during a period of three years, without apparent harm.

The chief manifestations of toxicity from the oral administration of cobalt in our experience were, as reported by others, referable to the alimentary tract: anorexia, heartburn, nausea and vomiting. In many patients receiving 300 mg. daily these symptoms were minimal or absent, but in some they were a very real obstacle to the administration of the therapeutic agent. The promptness and consistency with which each of 12 patients with pernicious anemia in complete remission experienced severe symptoms referable to the gastrointestinal tract suggest that the typical achlorhydria or rapid emptying time of the stomach was responsible and may occasionally condition similar undesirable side effects in other patients.

A patient with chronic lymphatic leukemia was given an intravenous injection of 50 mg. of cobaltous chloride dissolved in 250 cc. of sterile physiologic saline solution on sixteen occasions during a period of thirty-seven days. Whenever a given rate of infusion was exceeded, he experienced burning sensations and flushing of the face. However, if two hours was allowed to elapse for the entire injection, little difficulty was encountered. On one occasion when 75 mg. of cobaltous chloride was given to this patient intravenously, an episode of nausea, vomiting and bone pain occurred. No pathologic changes appeared in the urine of this patient or of any of the other patients during the period of cobalt administration.

Two patients, 1 with reticulum-cell sarcoma and the other with giant-follicle lymphoma, after being under treatment continuously with cobalt for one and two months, respectively, complained of severe substernal pain, which they attributed to the drug. In the first patient (Case 20), who was sixty-five years of age, the pain disappeared when cobalt administration was stopped for a few days, only to return when the therapy was resumed. An electrocardiogram was normal at the time, but when autopsy was performed four months later, an old septal infarct was found. In the second patient, aged fifty-eight years, the electrocardiogram was consistent with myocardial infarction. It seems doubtful that the cobalt administration was responsible for the production of the infarct, but it is understandable that the drug could give rise to symptoms in patients who probably already possessed an insufficient blood supply to the myocardium, especially if the fundamental action of cobalt salts is to interfere with intracellular respiration.[10]

As with any therapeutic agent, the possibility of injury from cobalt must be balanced against the urgency of the need for the drug. No one questions the use in skilled hands of irradiation or of war gases in the treatment of leukemias or other neo-

plastic conditions. These agents are frequently effective and though dangerous are less so than the uncontrolled disease against which they are directed. With cobalt there is perhaps little evidence of toxicity, at least after oral administration, other than irritation of the alimentary tract. However, we have found that there is also little probability of benefit in severe types of anemia otherwise unamenable to therapy. In mild anemias associated with chronic infections, the benefit due to the slight increase in hemoglobin that can be confidently expected may well be offset by the loss of appetite due to the drug. For these reasons, the clinical use of cobalt should probably be confined to cases of anemia in which other methods of treatment are clearly of no value. Thus, there is no indication for the use of cobalt as an adjuvant to liver extract or iron therapy. Moreover, it is likely that by critical determination of the daily level of reticulocytes during a period no longer than a week, the probable usefulness of the drug during a more protracted exhibition in any given patient can be assessed.

Summary

The daily oral administration of 300 mg. of cobaltous chloride to 17 patients without anemia produced slight reticulocyte responses in all within a week. Of the 10 patients given the therapeutic agent for over four weeks, moderate increases in red blood cells, hemoglobin and hematocrit were observed in all but 1.

Similar doses of cobaltous chloride were given for more than four weeks to 20 patients with various types of anemia refractory to other forms of therapy. In 2 of 5 patients with moderate anemia associated with chronic infections, in 1 of 2 patients with hypochromic anemia associated with inoperable carcinoma of the stomach and in 1 patient with familial microcytic (Cooley's trait) anemia, definite reticulocyte responses and rises in red-cell, hemoglobin and hematocrit values were observed.

In only 3 of 10 patients in the lymphoma group — 2 with reticulum-cell sarcoma and 1 with chronic lymphatic leukemia — was even suggestive evidence of ability to maintain higher erythrocyte and hemoglobin levels obtained. In none of 5 patients with refractory anemia and hypercellular bone marrow was erythropoiesis detectably affected. In 1 patient with the anemia of cirrhosis of the liver no response was obtained in an adequate trial. In 2 patients with anemia associated with chronic renal failure, given the drug for only a few days, no evidence of a reticulocyte response was noted.

Red blood cells produced by a patient during eleven weeks of treatment with cobalt contained spectrophotometrically normal oxyhemoglobin and survived normally when transfused into another patient.

In some patients the usual dose employed, 100 mg. of cobaltous chloride thrice daily, caused anorexia or mild symptoms referable to the alimentary tract. In a few cases these symptoms developed only after the medication had been administered for several weeks. However, the same amount of drug in each of 12 patients with pernicious anemia in maintained remission at once caused nausea and vomiting sufficiently severe to result in prompt abandonment of the medication. In another patient similar intolerance developed after two weeks when 400 mg. had been given thrice daily. Two patients fifty-eight and sixty-five years of age experienced precordial pain while being given 100 mg. of cobaltous chloride thrice daily and exhibited clinical evidence suggestive of myocardial infarction. All types of symptoms were relieved within a few hours by discontinuation of the medication.

The possibility that the erythropoietic action of the drug depends upon a fundamental alteration of tissue respiration indicates the need for further studies of chronic toxicity in animals and clearly suggests that cobalt salts should be used in man only in the treatment of anemias resistant to accepted forms of treatment and then with caution.

We are greatly indebted for the opportunity to study some of the patients to Dr. Walter E. Barton and his staff at the Boston State Hospital, Mattapan, Massachusetts, and likewise to Drs. Maurice B. Strauss and Charles R. Blackburn, of the Cushing Veterans Administration Hospital, Framingham, Massachusetts. Appreciation is also due Miss Phyllis Gordon for the performance of many of the blood examinations and to Miss Theo Wood for others, as well as for the preparation of the figures.

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METHODS OF INDUCTION IN PEDIATRIC ANESTHESIA*

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IN INFANTS and children the technic of induction of anesthesia demands careful consideration, if optimal results are to be obtained.

The success of the induction depends upon several factors, one of the most important of which is the preoperative handling of the child. The first objective is the elimination of fear. Intelligent parents can help in this by instilling confidence in their children, and convincing them that the doctors and nurses are going to help them. Much of this reassurance can be given at home before departure for the hospital. The hospital routine should be planned to avoid frightening the child. He should be admitted to the hospital at least the day before operation. This allows time to recover from being separated from his parents, and to become accustomed to hospital personnel and procedures. It also provides opportunity for adequate, leisurely workup. After a quiet night's sleep the child goes to the operating floor in a far more receptive state of mind than one who has been hurried into the hospital on the morning of operation.

The anesthetist should visit the child at least once before the operation. Receptive children may be told and reassured about what will take place at the time of induction. This calls for careful interpretation, not falsification. Preoperative medication is selected carefully at this time. Preoperative sedation is essential for all children who are old enough to become emotionally disturbed. Gentleness and finesse can do much to gain the co-operation of the frightened child, but a far greater kindness is done the child if adequate medication is relied upon for the major part of the effect.[1, 2] The dosage of preanesthetic drugs cannot be dictated arbitrarily, since many variable factors are concerned. Approximate dosages for healthy children are presented in Table 1. Children should arrive on the operating floor calm and drowsy. Here they should await surgery in a quiet room and with an attendant. The sleeping patient should not be disturbed. The others may be watched or quietly amused. Every attempt should be made to prevent them from becoming upset at this time. Such preparation, when successfully carried out, greatly increases the chances for an easy induction.

The choice of the agent and technic of induction depends upon the individuality of the child. Although all children are different, it is possible to make a rough classification into groups that have certain definite characteristics.

TABLE 1. *Approximate Dosage of Preanesthetic Drugs.*

AGE OF PATIENTS	WEIGHT	ATROPINE	MORPHINE	NEMBUTAL
yr.	*lb.*	*mg.*	*mg.*	*mg.*
Newborn ...	7	0.065	—	—
1	21	0.13	1.0	35
2-4	27-35	0.18	2.0	50
4-6	35-45	0.22	2.7	65
6-8	45-55	0.26	4.0	100
8-10	55-65	0.32	5.4	130
10-12	65-80	0.36	8.0	160

INFANTS UNDER ONE YEAR OF AGE

Small babies require relatively little psychology in their handling in the operating room. They are usually hungry, and though they may sense the strangeness of their surroundings, they certainly have no apprehension of the impending procedure. In young infants the metabolic rate is relatively low,[3] whereas the threshold of pain is high. Consequently, sedative drugs are not indicated. Atropine is used to prevent excessive secretions and to block vagal reflexes. If the babies cry preoperatively, they may be picked up and comforted so that they will not become tired or emotionally disturbed. It has been found that an infant's stomach may become distended after a crying spell.

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Some anesthesiologists advocate the use of such technics as spinal anesthesia, or pentothal and curare on small babies. Although unusual circumstances occasionally indicate the use of one of these methods, their routine usage in the small infant seems, in my experience, to be uncalled for and even dangerous. The smaller and weaker the baby, the simpler should be the methods used. The respiratory reflexes should be depressed as little as possible, and normal function should be encouraged. The most readily controlled drugs should be chosen rather than those of a lasting effect.

Although ether may be used safely for induction of small infants, it is so irritating that it may cause prolonged struggling and breath holding. Ethyl chloride is less irritant and produces rapid induction, but its toxic effect on the heart renders it undesirable. Divinyl ether, or vinethene, although toxic if used over a long period, is a safe inducing agent. It is more potent than ethyl ether and is less irritating. It increases the respiratory exchange, and does not cause reflex spasms. It appears to be the agent of choice for the induction of healthy infants and young children.

At the time of induction, the infant's clothes are loosened so that he may breathe and move freely. Since young patients are frightened if their eyes are covered, this practice is not carried out until they are asleep. A baby Yankauer mask with only four layers of gauze is employed. Holding the mask down over the infant's chin, the operator drops the anesthetic slowly at first, so that this new odor is introduced gradually to the patient. The mask is brought slowly upward over the mouth and nose until full concentration of the agent is reached. There is then usually thirty seconds to a minute of resistance and crying, after which the infant falls into rapid, full, regular, respiration and exhibits increasing muscular relaxation. At this time it is important not to administer the vinethene too rapidly, for such a procedure may cause a characteristic clonic motion. The patient should be held in light anesthesia with vinethene as the ether is gradually introduced. After thirty to sixty seconds a sufficient concentration of ether will have been established, and the vinethene may be discontinued. Vinethene-ether inductions average three or four minutes for infants.

Induction is facilitated if the infant cries and moves his arms and legs, for these activities promote the respiratory exchange. These patients rarely show evidence of passing through an excitement stage, nor do they vomit during induction. Certain members of this younger group, however, will quite confound the anesthetist. Instead of crying and struggling, they lie still, limiting their breathing to a minimal exchange, and even after fifteen minutes under an ether mask, they may still be rigid and awake. Such infants can often be induced to move and cry if the anesthetist gently rubs their faces, passively moves their arms and legs or lightly massages their ribs. The most difficult patient is the baby who refuses to breathe at all under the anesthetic mask — he simply holds his breath. In such a case cyanosis quickly appears, and it is dangerous to attempt to outlast such a resistant infant. If two or three attempts at induction with a volatile anesthetic are fruitless, one should choose a less irritating agent.

Cyclopropane is very useful for induction of anesthesia in this young age group.[4] Infants breathe it readily and with little struggling or breath holding. For this reason it is the agent of choice in ill, premature and resistant infants. However, cyclopropane has several characteristics that preclude it from being the first choice in all cases. Respiratory depression may occur, or a marked respiratory spasm with its resultant retraction of the ribs. Once a patient has been induced with a volatile anesthetic, the succeeding anesthesia level is easily stabilized, but with cyclopropane this level is maintained with more difficulty. The explosive hazard of this agent and the management of special equipment for its closed system administration are factors that should influence the anesthetist to elect the simpler methods.

There is a specific type of case worthy of mention: the infant with pyloric stenosis. As the pylorus is obstructed, there is almost always a large residue in the stomach. Not only is induction especially difficult in such cases, but also the operative procedure is made dangerous, for regurgitation and aspiration of stomach contents are frequent. Induction will be much easier and operation safer, if a small tube is passed through the nose and the stomach emptied *before* anesthesia is started. This should be performed on all patients with distention and upon healthy children who are suspected of having eaten recently.

Children One to Three Years Old

Children in this age group are relatively sturdy and have elevated metabolic rates. Morphine is indicated for its analgesic effect, as well as for the purpose of lowering the metabolic rate. Although young children will usually not have definite fears concerning an operation, they are easily frightened and hard to control. Barbiturates are tolerated well and may be used to help sedation of active young children prior to induction with inhalation agents. Nembutal may be given an hour and a half before operation, and morphine and atropine forty-five minutes preoperatively.

An earnest attempt should be made to gain the confidence of these children by preoperative attention on the ward and in the waiting room. For patients who appear moderately co-operative, vinethene offers the advantages of simplicity, speed and safety. There will usually be resistance to any method of induction. Needles cause the greatest

disturbance, and the small veins offer targets that are not easy to hit. In general, there is less resistance to the cloth mask and vinethene than to the more bulky closed-system apparatus needed for the less irritating agents. The administration of any agent should be gentle but, once begun, should progress actively. Any faltering or lapse on the way may cause spasm or retching and will result in a prolonged excitement stage and excessive secretions. It is especially important to maintain unobstructed respiratory exchange during this phase of anesthesia. The patient's chin must be supported at all times, and a suitable airway and suction used when indicated. However, since any prolonged removal of the anesthetic mask during induction may allow rapid lightening of anesthesia and further complicate the picture, suctioning and so forth must be performed as rapidly as possible.

Children in this group cannot be reasoned with effectively. If they become frightened they may struggle and scream so actively during induction that sobbing, jerky respiration will continue long after full anesthesia is established. For the child who appears excited and is resistant, rectal anesthesia is undoubtedly the most successful. There is not the pain of the needle, and there is no odor nor mask. A smooth, uncomplicated induction is almost certain. If morphine has not been administered, avertin in doses of 80 to 100 mg. per kilogram of body weight will give excellent basal anesthesia with a minimum of respiratory depression.[5] It should be emphasized that serious respiratory depression may follow the combined use of morphine and avertin. If a sedative has been given with only partial effect, pentothal by rectum can be used to similar advantage.[6] A 0.6 per cent solution of pentothal is easily prepared by a mixture of 0.5 gm. in 75 cc. of water; 2 cc. of this solution per pound of body weight will quiet an active child, and make induction rapid and easy.

Although rectal anesthesia may seem the technic of choice in most cases, there are definite drawbacks. Children who are to receive avertin should have no other preoperative sedation; therefore, their stay on the operating-floor waiting room is apt to be most upsetting to them, as well as to those nearby. Another point against avertin is that it is mildly irritating and frequently acts as a purgative. Pentothal does not have this quality, but, like other barbiturates, it is not consistent or predictable in sedative effect until large dosages are used.

If the child is receiving an intravenous infusion preoperatively, the anesthetist has an excellent opportunity to inject 2 or 3 cc. of 2.5 per cent pentothal into the intravenous tubing, and thereby effect a most pleasant induction. Cyclopropane may be called upon for the same uses as in the youngest age group — namely, for quick, nonirritating induction when indicated by special circumstances.

Children Three Years of Age and Over

In the group of healthy children three years of age and over, the preoperative preparation becomes especially important because fear, imagination and previous experiences, either of the patient or those told him by his ward mates, can cause havoc with the child's emotions. In addition to atropine and morphine in suitable dosage, a barbiturate should be given to all these patients who are to have inhalation induction. Comparatively large dosages of barbiturates are required for effective sedation, but these relatively large doses have proved remarkably safe and free from side effects.

This group offers a special challenge to the anesthetist, for it should be possible to put each patient to sleep without making him cry or struggle.[7] If the child is successfully medicated this can be done readily and with a wide choice of agents. Co-operative older children (five to ten years or over) are easily and pleasantly induced with nitrous oxide and oxygen or cyclopropane and oxygen anesthesia.

Some of these patients are apprehensive even after suitable premedication, and these require the most careful treatment. Five minutes devoted to putting a child into a better state of mind is time well spent. Most children of the preschool and school ages can be reasoned with if the proper avenue of approach is discovered. Those who have specific fears are often easily quieted if the subject of their concern is known and discussed. Many are afraid of being hurt, or of being put to sleep with ether. Others are afraid because they do not know what is going to happen to them, and some know what is going to happen and dread it. After a short attempt at rational reassurance, the anesthetist should actively divert the child's attention from the business at hand. The child's interest is easily turned to pleasant, familiar subjects such as his pets or his favorite hobbies.

The patient should be in a quiet side room for the actual induction. The anesthetic apparatus should be shown to the child and he should handle it, smell it and play with it. If this can be fitted into a game it is more readily accepted by the child. The apparatus may be used as a telephone or it may be described as a dream machine — one valve for dreams about ice cream, one for chocolate cake and so forth. Orange, lemon or peppermint flavors may be added to the apparatus at the patient's choice. If the child still shuns the apparatus, he may be allowed to make his own selection between open or closed mask, or intravenous induction. Frequently the opportunity to decide for himself will change his whole outlook on the procedure. The anesthetist will make it much easier for himself if he can start a story or game that has a definite continuity to it, and carry it throughout the whole induction. A song or story will help with the smaller

children; the older ones may be encouraged to count by threes or fives, or to do a similar task that requires real attention.

Restraints should not be used. Instead, children should be encouraged to use their hands to help hold the mask by themselves, or to hold an assistant's hand, but for companionship rather than restraint. An apprehensive child is not a good subject for nitrous oxide, since the relatively slow onset of anesthesia is apt to allow time for him to become frightened. In such cases, the more rapid induction with cyclopropane is an advantage in spite of its slightly greater hazard.

If there is a vein that looks easy of entry, a single needle puncture will effect an easy induction with pentothal (3 to 5 cc. in 2.5 per cent solution). It should be mentioned that although induction of sleep with pentothal is rapid and easy, respiration is depressed, whereas laryngeal reflexes remain active. If full surgical anesthesia is to be obtained later with ether, it is sometimes found that the initial use of pentothal results in slower induction than when other agents, such as nitrous oxide and vinethene, are used.

Patients with Complications

Patients who have complicating illnesses or are in poor general condition require special attention. Premature infants should not be subjected to volatile anesthetics. Cyclopropane provides a more gentle induction and gives adequate relaxation. In patients with elevated temperatures anesthesia can be induced with pentothal, and the patients can be maintained on cyclopropane, again with the avoidance of volatile anesthetics. The anesthesia in children with cardiac disease, such as patent ductus arteriosus, coarctation of the aorta and mild rheumatic heart disease, who are not cyanotic or in decompensation, may be induced as that in normal children. Those with cyanotic heart disease or with decompensation provide just cause for considerable concern. Adequate medication is of importance, for as sedation becomes more effective, oxygen demands decrease and the work of the heart is reduced. A marked improvement in the color of the blood is often observed when anesthesia is induced in properly medicated patients, even without the addition of oxygen. Usually, however, when one is dealing with cardiac patients, it is wise to saturate the blood with oxygen before the induction is begun. Then, pentothal-ether or cyclopropane-ether sequences may be administered with minimal excitement and hypoxia, and have proved to be effective methods of induction.

Anesthesia for Outpatient Operations

Strangely enough, the group that presents some of the most difficult problems, and perhaps the greatest possibility for tragedy, consists of healthy children who come into the outpatient clinics for such minor ailments as a cut finger or a fractured wrist. These children may have eaten liberally shortly before admission, and, of course, they are badly upset, both by the accident and by the trip to the hospital with their equally unstrung parents.

The traditional treatment received by such children included their being pricked with a needle, then after a long, fearful wait, being pulled away from their parents and forced down on a table under an ether mask. The noise of the ensuing struggle could easily be heard, and usually was, by the parents in the waiting room. Under such conditions induction was accompanied by intense, prolonged excitement, and also too often by copious vomiting and possible aspiration. The relaxation for surgery was poor, and after the operation the recovery period might involve several hours more of nausea and vomiting.

Unfortunately, relatively few surgical procedures can be done humanely on children under local anesthesia alone. General anesthesia is necessary, but in outpatient surgical operations in children ether should be avoided, owing to the danger of aspiration of vomitus. Although cyclopropane may appear to some to be the agent of choice for such work, its explosive danger seems to contraindicate its routine use for minor surgical procedures. Treatment of patients entering the hospital for operation with a full stomach has long been a serious source of danger. Several courses of action are open. Passage of a stomach tube rarely results in removal of the larger, more dangerous pieces of food. Methods to make the child vomit preoperatively are often terrifying. Waiting a prescribed period for digestion of food is usually ineffective. Still another method is to induce anesthesia rapidly with cyclopropane and pass an endotracheal tube — rather a major anesthesia for a minor operation. I prefer to avoid the use of ether and cyclopropane in such cases. My method of choice is to use a combination of agents that effect an easy induction and maintenance of anesthesia without irritation of the vomiting reflexes. Induction can be accomplished very well with avertin. The parents should be allowed to stand by and witness the gentleness of the procedure. After the child is asleep he may be carried into the operating room. There, light nitrous oxide-oxygen, supplemented, if necessary, by block anesthesia, will be adequate for most such minor procedures. The patient will usually react at the end of operation and be ready for discharge in half an hour, having been subjected neither to discomfort nor to danger. Procedures requiring only momentary anesthesia may be done under vinethene alone. Longer operations on older children may be done under intravenous administration of pentothal with nitrous oxide, but for most outpatients the combination of

avertin and nitrous oxide and local anesthesia will be found most advantageous.

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MEDICAL PROGRESS

ORAL SURGERY (Concluded)

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The Surgical Correction of Jaw Deformities

In children many jaw deformities can be treated by means of orthodontic procedures. Later in life, or if the deformity is severe, surgical correction may give excellent cosmetic and occlusial results. The deformities referred to are mandibular protrusion (prognathism), mandibular retrusion (underdevelopment or micrognathia) and open incisor bite or apertognathia. These deformities are frequently of congenital origin, often inherited (Hapsburg jaw), or acquired through malunion of a fracture, underdevelopment as in early cases of ankylosis or overdevelopment due to such diseases as acromegaly or leontiasis ossea.

One of two sites may be selected for the operative correction, the ascending ramus and the body of the mandible. For prognathism and mandibular underdevelopment both operations have their champions. For correction of apertognathia, the operation in the ramus is not suitable because closing the occlusion would cause distraction of the osteotomized ramus, and the action of the elevator muscles would cause recurrence.

The operation performed in the ascending ramus is a bilateral osteotomy, whereas in the body of the mandible an ostectomy is used for setting the jaw back in protrusion or closing it in open bite. For advancing the jaw in retrusion, a sliding, Z-shaped osteotomy is recommended.[135] If the jaw is protruding without open bite, a parallelogram is excised; if an open bite is also present, a wedge-shaped or rhomboid-shaped piece of bone has to be removed to allow, through angulation, the closing together of the anterior teeth. Thoma[136] presents a diagram that shows how the size of this piece of bone may be geometrically determined.

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The following authors have recommended osteotomy in the ascending ramus for repositioning of the jaw: Babcock,[137] Hensel,[138] Smith and Johnson,[139] Hook and Taylor,[140] Ivy,[141] Traynham,[142] Moose,[143] Lloyd,[144] Stetzer,[145] Peterson[146] and others. Those who prefer an ostectomy in the body of the mandible are New and Erich,[147] Cameron and Stetzer,[148] Dingman,[149] Kemper,[150] Thoma[151] and others. Those who use both procedures are Kazanjian[152] and Waldrom.[153]

An excellent discussion of the advantages and disadvantages of each method was given by Dingman.[154] He wrote that correction of the deformity and repositioning of the teeth may be accomplished by either osteotomy or ostectomy.

Osteotomy is accomplished by a transverse division of the ramus of the mandible and shifting of the bone backward, or forward, where it is held in position during the course of healing. The procedure is simple to execute, avoids the possibility of injury to the inferior alveolar nerve and does not entail sacrifice of useful bone, nor does it damage the mandibular arch or teeth. The operation can be done without contamination from the oral cavity, by means of a Gigli saw, or by open operation with an incision below the inferior border of the mandible. The obvious disadvantages are that a parotid fistula may form. Injury to the facial nerve and serious hemorrhage from the internal maxillary artery may occur. There may be derangement of the muscles of mastication. The possibility of over-riding of the fragments, nonunion, malunion and open-bite deformities must also be considered very serious disadvantages. It is more difficult to adjust bite irregularities when this method is used.

Ostectomy has many advantages. The site of operation is extremely accessible, and the bone section can be removed without interference with the inferior alveolar nerve or its associated structures. The operation also does not interfere with the muscles of mastication; fragments can be repositioned more accurately and satisfactorily. A

dental splint, fitted to the mandible, often holds the fragments in place after very short periods of intermaxillary fixation. The only objections to the procedure are that it necessitates the sacrifice of one or two teeth on each side of the mandible, if an edentulous space does not already exist. It also necessitates the sacrifice of a section of mandibular bony structure. The fact that ostectomy offers almost uniformly successful results with a minimum of effort and only slight possibilities of complications indicates that this is the method of preference in most cases.

Osteotomy in the neck of the mandibular condyle was recommended by Schaefer.[155] He performed the operation with a Gigli saw inserted through short skin incisions.

Another operation, called the "bow-back operation," was described by Pettit and Walrath.[156] It was originated to correct unilateral prognathism, but can be used for bilateral cases as well. The authors perform an osteotomy in the surgical neck of the condyle that allows the jaw to be set back. The jaw is wired in this position for three weeks if fascia has been inserted between the fragments to form a false joint, or longer if bone union is desired. The advantage of this procedure is that it eliminates most of the objections raised against the other methods, but it seems to me not applicable to the correction of very extreme cases or to cases with open bite. For the correction of prognathism, a similar method was recommended by Smith and Johnson[139] and has since been perfected by Smith.[157] In suitable cases he removes a parallel epipedonal section from the region of the sigmoid notch for transpositioning of the condyle.

Cysts of the Jaws

Cysts of the jaws and mouth are generally classified according to their pathogenesis. The most important is the group of developmental cysts formed from odontogenic tissues and called odontogenic cysts. Other cysts occur from nonodontogenic tissue; they are caused by enclaved epithelium (fissural cysts[158, 159]), or by epithelial remnants such as those found in the nasopalatine duct (incisive canal cysts[160, 161]). In addition, there are extravasation cysts[162, 163] of traumatic and nontraumatic hemorrhagic origin. Robinson[164] has recently presented a classification compiled after discussion and consultation with surgeons, radiologists and pathologists of note.

A large literature exists describing not only the various types of odontogenic cysts but also their anatomic distribution. They may be found in the tooth-bearing part of the mandible as well as the ascending ramus. In the maxilla they may encroach upon the nose or displace partly or completely the maxillary sinus. Cysts have often a hereditary history and then occur also in multiple form in the individual person.[165]

The neoplastic potentialities of such cysts are important, the epithelial lining having been reported to give rise to adamantoblastoma forming mural thickenings first and invading the jaw widely later.[166, 167] Cysts in which an epidermoid carcinoma developed were seen by Simmons[168] and Kent.[169]

To facilitate roentgenologic diagnosis, aspiration of the cystic fluid and replacement with a radiopaque substance have been recommended as being especially useful for maxillary cysts.[170, 171]

The treatment consists of complete enucleation of the cyst membrane, though there are some who prefer marsupialization or a modified Partch operation.[172-174]

In these procedures the main part of the membrane is left in situ to protect the roots of involved normal teeth until, because of the evacuation of the cyst fluid, the cavity has become gradually eliminated. This method has the disadvantage of leaving behind pathologic tissue, perhaps with tumor or potentialities to form it, and, therefore, is not accepted as good practice by others. A new procedure combines the complete removal with the preservation of the involved teeth and, since it makes closure of the incision possible, eliminates prolonged postoperative treatments and irrigations to remove food from the recessed area. This procedure consists of space elimination by means of fibrin foam. It was recommended by Thoma[175] and utilized by him[176] and others[177] for filling the bone cavity after removal of the cyst sack with material that prevents the formation of a large blood clot, which would break down and permit healing by the formation of fibrous tissue and bone. The fibrin or gelfoam, soaked in a solution of thrombin and penicillin, is inserted, and the wound closed with closely placed, interrupted sutures. Both involved teeth in dentigerous cysts and adjacent teeth can be saved,[178] and if in a young person a partly formed tooth is accidentally removed with the cyst sac, it may be replanted with success,[176] since the pulp of such teeth with large apical foramens will become revascularized and will continue to develop and erupt.

Tumors of the Mouth and Jaws

A great variety of tumors that occur in the mouth may be classified roughly as follows: tumors of the soft tissues of the oral cavity; peripheral tumors of the jaws; osteogenic tumors of the jaws; tumors of the jaws of odontogenic origin; and central tumors of the jaws of nonosteogenic and nonodontogenic origin. Like tumors in other regions, these growths may be benign or malignant, either with local invasive tendency or producing metastases.

To review what has been published on the diagnosis, pathology, treatment and aftercare of these tumors is beyond the scope of this article. The discussion is therefore limited to the more unusual cases

reported during the past ten years, a collective review on the subject having been published in 1938.[179]

Hyperplasia

A large number of the oral tumors are not true neoplasms but are hyperplasias that develop because of chronic irritation from ill fitting dentures and malhygiene.

Benign Giant-Cell Tumor

This lesion occurs as the so-called giant-cell epulis, a peripheral tumor found on the alveolar process and as the more important central type. Central giant-cell tumors are not rare in the jaws. They occur less commonly in the maxilla[180, 181] than in the mandible. In the latter, they are found most frequently in the symphysis,[181] but may occur anywhere.[182]

In children a frequent place of development is at the site of resorption of the deciduous teeth.[183] Conservative curettage is recommended,[184] followed by cauterization with phenol. A review of the literature has been made by Bernick.[185] The relation of these tumors to parathyroid activity is of interest. The statement is unwarranted that all benign giant-cell tumors are due to increased parathyroid activity,[185] but it is essential that there should be a careful investigation of the blood chemistry, and the skeleton should be investigated by x-ray examination. A giant-cell tumor that was caused by hyperparathyroidism and receded after excision of the parathyroid tumor was recently reported.[183]

Fibroblastoma

Oral fibromas are quite common. They occur in any part of the mouth and are also seen as central tumors in the jaws. These are frequently ossifying fibromas. A case involving almost the entire subdental area of the mandible was reported in a woman forty-one years of age.[104] She complained of periodic pain but she did nothing about it until her cheek and lip had become numb and her teeth sore.

Fibrosarcoma

Fibrosarcoma is much less common. It occurs as a peripheral and as a central tumor. The malignancy varies somewhat. In a sixty-year-old man, a fibrosarcoma of the mandible, which was of moderate size but caused a pathologic fracture, recurred after resection of the jaw and caused lung metastasis.[186] A similar case,[187] which was of five years' duration and was entirely asymptomatic, was seen in a sixteen-year-old girl. The affected segment of the jaw was resected, and a bone graft was later inserted. There was no recurrence after two years. Not so fortunate was the outcome in a seventeen-year-old boy.[188] The tumor was of six years' duration and was treated by x-ray therapy. When it did not regress, the jaw with a mass extending from the canine to the molar region was excised. After a year, it recurred locally, extending into the left cheek, nose, temporal region and frontal, sphenoid, and orbital bones. The patient died sixteen years after onset. A rare case of a fibrosarcoma arising from the capsule of the mandibular joint and causing excruciating pain for three years gave a great deal of difficulty in diagnosis. The patient was seen by many specialists. Disease of the ear and Costen's syndrome were thought of, but at an exploratory operation, a fibrosarcoma was found. It was removed by means of a condylectomy and after a year and a half there had been no recurrence.[183]

Myxoma

Thoma and Goldman[189] report that this tumor has hitherto been regarded as similar to those in long bones, which tend to recur and are often malignant. A study based on 7 cases shows the jaw tumor to be benign, perhaps because it is of odontogenic origin. It is often associated with embedded[190] or with missing teeth and may have the x-ray appearance of a dentigerous cyst. It may be regarded as an odontogenic fibroma that has undergone myxomatous degeneration. The x-ray film generally shows a honeycomb appearance,[189] but the tumor may be cystic with an irregular, lobulated outline.[189, 191] A large myxoma expanding the bone was reported in the symphysis mandibulae.[192] The maxilla is also often involved[189]; it may involve the entire half.[193] A very unusual myxoma was reported in the mandibular condyle.[194] It had been found in a forty-eight-year-old woman with Ménière's disease. For four years she had felt a swelling in front of the ear that had caused limitation of motion and pain. X-ray films showed a globular enlargement and trabeculation of the condyle, and after excision a diagnosis of fibromyxoma was made.

Neurofibroblastoma

Benign neurofibromas are peripheral or central tumors, forming from the nerves that pass into the bones and supply the teeth. A neuroma has been reported as occurring on the palate of a fifty-five-year-old man.[195] It formed at the site of the larger palatine foramen. A neurofibroma forming a cystic defect, which in the x-ray film was seen to extend in the subapical area from the mental foramen to the ramus, was reported in a man aged thirty-three years.[196] It was diagnosed as a radicular cyst. It healed promptly and uneventfully. Another neurofibroma,[195] developing after a tooth extraction, encroached upon the maxillary sinus and invaded the zygomatic fossa. Martin[197] reported 2 cases. These were both cases of generalized neurofibromatosis with bulky invasion of the oral cavity. In 1 case, that of a three-year-old boy, the diagnosis was plexiform neurofibroma, which was slowly progressing and benign. In the second case, a girl five years old, the local tumor took on malignant, locally invasive characteristics and

resulted in death. Autopsy revealed no sign of general dissemination. An adrenal neuroblastoma in a two-year-old child was reported by Burford.[198] Six weeks before examination, a small, nontender lymph node was found in the right submaxillary area. Bilateral orbital ecchymosis developed next, with considerable enlargement of the side and face and neck on the right. Extensive osteolytic and osteoblastic changes were found in the entire skeleton. Biopsy from the buccal mucosa disclosed an unclassified malignant tumor. The patient died eight days later. At autopsy, a neuroblastoma of the right adrenal gland was found, with widespread involvement of lymph nodes, bones and retro-orbital region.

Lipoma

This is an uncommon and perfectly benign tumor, which may form beneath the mucosa and produce a yellowish, soft tumor mass that is sometimes lobulated. More difficult to diagnose are lipomas occurring in the floor of the mouth beneath the sublingual gland, or in the infratemporal fossa. Here they may interfere with the motion of the ramus of the mandible. A case of this type was reported by Thoma.[199]

Hemangioma and Lymphangioma

An intraoral nevus, occurring on the maxillary gingiva and of grayish-pink color, was reported by Field and Ackermann.[200] Burford et al.[201, 202] state that cavernous hemangiomas of the oral cavity are relatively common. They are easily recognized by their grayish-blue color. Their report includes a large hemangioma of the lower lip in a thirty-two-year-old woman who was successfully treated with sodium morrhuate (5 per cent) injections. Another case reported from the same clinic[201] occurred on the upper lip in a nineteen-year-old Negress. This tumor was excised by ligation of two large vessels at the labiolingual fornix that entered the tumor mass. Thoma[183] described a hemangioma occurring in a fifty-nine-year-old woman and containing phleboliths that could be felt in the cheek and were demonstrable in x-ray examination. Erich[203] reported a central hemangioma of the mandible, which caused intermittent stabbing pain and formed a cystic-appearing lesion that had the x-ray appearance of a giant-cell tumor. Lymphangioma usually occurs on the tongue and is frequently congenital, producing macroglossia,[204] which, of course, is not a pathognomonic term. In a case reported by Rigg and Waldapfel[205] the tumor occurred in two separate areas.

Hemangioendothelioma

This tumor was discussed by Cheyne and Silberstein,[206] who, after reviewing the literature, reported 3 cases: in an eight-year-old boy with a tumor on the lower lip, in a fifteen-year-old girl with a growth on the roof of the mouth, and in a sixty-seven-year-old woman with a mass on the right side of the palate. All were studied pathologically. The authors state that clinically the tumor is generally an infiltrative growth, in some cases slowly growing and benign, whereas other hemangioendotheliomas, which are avascular, show greater metastasizing ability. The lesion is generally amenable to proper surgical removal.

Myoblastoma, Rhabdomyoma and Leiomyoma

These are rare tumors, occurring principally in the tongue. Myoblastomas, known as "rhabdomyoma granulocellulaire" in the French literature, are also found in the lip, soft palate, pharynx, uvula and jaws. Mann and Ash[207] reported a case on the gingiva of both the maxilla and the mandible of a two-week-old infant. Thoma[208] reported one excised from the tongue of a thirty-year-old woman. Considerable speculation exists regarding the etiology of myoblastomas. The controversy was discussed by Bernier,[209] who, analyzing 17 cases,[210] concluded that a number of tumors reported as myoblastomas on closer examination are rhabdomyosarcomas. Myoblastomas are small — seldom larger than 1.5 cm. in diameter.

A leiomyoma of the tongue occurring in a thirty-two-year-old Negro was surgically removed and was thought to be derived from the smooth muscle of the blood vessels. It appeared to invade the mandible at the angle.[201]

Osteoma

Some osteomas, which are in reality bony hyperostoses, occur quite frequently on the palate, (torus palatinus) and the mandible (torus mandibularis).[211] The head of the condyle occasionally becomes enlarged — a condition that has been variously reported as hyperplasia and osteoma of the condyle.[212, 213] True osteomas occur peripherally on the oral[214] or cutaneous parts of the jaws,[215] and also as central tumors.[183] Sometimes multiple osteomas are found, generally in connection with similar formations in other parts of the skeleton.[216]

Fibro-osteoma

This tumor is generally classified as an ossifying fibroma,[196] a term that is often used for a fibroma in which a certain amount of bone is produced but in which the bone plays an unimportant role, whereas "fibro-osteoma" is reserved for a tumor with typical clinical and histologic characteristics. This lesion has been called various names such as osteofibroma and fibrous osteoma, and some pathologists tend to consider it not as a neoplasm but as a bone dystrophy that gives rise to such names as localized osteodystrophia, localized osteitis fibrosa and fibrous dysplasia. Cahn[217] states that fibrous dysplasia is an expansive lesion with thinning of the cortex and no periosteal reaction. There is a replacement

of tissue within the bone. If there is considerable calcification, the radiopacity may suggest an osteomatous growth.[215] On the other hand, if the replacement tissue has irregularly eroded and distended the cortex resulting in bony ridges on the internal surface, the x-ray picture may look monocystic[194] or multicystic or may resemble a central giant-cell tumor or adamantoblastoma. Schlumberger[218] concludes that ossifying fibroma is a variant of monocystic fibrous dysplasia. The lesion may involve one or both sides of the maxilla or may affect the mandible — in some cases all three. I believe that it is a tumor of medullary origin in which the tumor cells produce, by metaplasia, fibrous connective tissue in which osteoid is deposited irregularly in some[219] and as trabeculae in other cases.[215] The tumor is calcified partially in young and completely in older persons when it frequently ceases to grow. Furedi[220] groups these lesions into hypostotic and hyperostotic.

Chondroma

This osteogenic tumor is rather rare. Jacobs[221] reported a cystic osteochondroma of the mandible that showed no recurrence three years after excision.

Osteogenic Sarcoma

Cases of both primary and metastatic types have been reported. The former includes a case that occurred in the maxilla[222] of a twelve-year-old girl and involved the antrum and occluded the nostril, and was treated by excision and x-ray irradiation. Another[223] occurred in a forty-year-old woman, and grew slowly until it filled the entire vault of the palate. It was diagnosed as an osteogenic chondrosarcoma. A case [224] that developed in the mandible was treated by resection of half the mandible. There was no evidence of recurrence a year later.

Of the metastatic cases, 1 was found in the maxilla, and 2 in the mandible. That in the maxilla[225] occurred in a thirteen-year-old girl with a primary osteochondrosarcoma of the right tibia, which was treated by leg amputation, and a secondary tumor of the same type on the left femur, which was similarly treated. Six months later a swelling of the tuberosity of the maxilla appeared that was identical with that of the previously occurring tumors of the extremities.

The first of the mandibular metastases,[226] which occurred in a twelve-year-old boy five months after a diagnosis of primary chondroblastic osteogenic sarcoma had been made, followed an injury (bruise) of the inner aspect of the tibia the month before. He was treated by irradiation. The metastasis occurred below the second molar. When the tooth was extracted the diagnosis was made from tissue attached to it. The other metastasis occurred in an eleven-year-old boy[227] with osteogenic sarcoma of the tibia, which was treated by leg amputation. Four months later a tumor formed in the third molar region invading the bone and pulp of a tooth.

Odontogenic Tumors

These tumors may be formed either from the epithelial component of the tooth-forming organ or from the mesenchymal part. In some cases — the mixed odontogenic tumors — both are involved. The following types are of interest:

Adamantoblastoma. This lesion is considered a benign tumor that is locally invasive. A case with metastases to the lungs has been reported by Schweitzer and Barnfield.[228] An adamantoblastoma was excised by removal of a section of the left mandible. Seven years later the tumor recurred in the ascending ramus and was treated with radium. It continued to grow, and involved the skull. Four years later, x-ray films revealed metastasis to each lung field. Two years later the patient died from local hemorrhages at the age of thirty-six years. An autopsy report was appended to the article.

Of the 16 cases reviewed for this article,[229] 14 occurred in the mandible, and 2 in the maxilla. One of the latter formed a bulky enlargement of the lateral half of the alveolus of a seventy-two-year-old man. It extended to the maxillary sinus and nasal fossa. It was a polycystic tumor that could be completely excised. The other case[167] was that of a seventeen-year-old girl who on roentgenologic examination appeared to have a dentigerous cyst filling the antrum. When enucleated, the growth was found to contain epithelial elements that had formed coarse papillary projections and ill defined cysts.

The mandibular cases were either monocystic or polycystic. The monocystic tumors resembled either a follicular cyst[196, 230] (without tooth) or a dense dentigerous cyst.[167, 196] The polycystic tumors may form two or three large compartments or are definitely polycystic (soap-bubble effect)[183,196,198] and may perforate.[232] Generally, the tumor forms in the molar region and invades the ramus,[196,229] but it may also occur in the anterior part of the mandible.[200] Some of these tumors expand the bone to cause considerable asymmetry of the face,[233] or an intraoral mass, [229] and in some cases a large swelling develops, as in that reported by Burford, [198] in which the chin was enlarged by a voluminous tumor the size of a grapefruit.

Recurrence after enucleation is common. Many of the patients were treated for excision of a "cyst," which later recurred as a polycystic tumor.[183,229,232] That recurrence occurs even after resection, was brought out by the cases of Schweitzer[228] and Dingman.[234] Adamantoblastomas sometimes form in the dental follicle of an unerupted third molar,[235] which, therefore, should be removed when the tooth is extracted. Treatment by enucleation is indicated in some cases. Penhale[231] shows excellent filling in with bone two years after operation. In polycystic cases, excision of a section or resection of the affected

half of the mandible is recommended, followed by restoration of the jaw with a bone graft.[182, 232, 233]

Cementoma. This tumor is distinguished from odontoma by the fact that only one type of calcified tooth structure is formed. Cementomas occur more often in the mandible than in the maxilla. Bernier,[236] investigating 15 cases, of which only 1 occurred in the upper jaw, found that their structure varied. Ten were trabeculated, and 5 were composed of cementicles. Many cases show multiple occurrence.[237]

Mixed tumor. These are made up of epithelial and mesenchymal elements. Thoma and Goldman,[238, 239] in a review of 75 cases, distinguished three types: soft odontoma, soft and calcified, and completely calcified. The last is known as odontoma.

Odontoma is made up of masses of tooth tissue that has become calcified. It is considered a very benign tumor that ceases to grow after all soft tissue has been replaced. A case has been reported of a tumor that caused a gradual increase in size of the jaw, with alteration of the occlusion.[240] Ordinarily these tumors are asymptomatic, even if large.[241] The excision is attended by the danger of fracture of the jaw. Therefore, in cases of extensive tumors, a two-stage operation is recommended by Callahan.[242]

The soft and partly calcified odontogenic tumors, on the other hand, may continue to grow. Both the epithelial components and the mesenchymal part have the ability of neoplastic proliferation. Thus the adamanto-odontoma forms, in which, besides dentine and cementum, epithelial cells are present, both as differentiated cells (ameloblasts), which form enamel, and as undifferentiated adamantine epithelium, which is neoplastic and locally invasive.[215, 243] In other cases the mesenchymal part may take on malignant characteristics (fibrosarcoma), and form a so-called adamantino-sarcoma.[244]

Mixed tumor of salivary-gland type. This tumor, also composed of epithelial and mesenchymal structures, is much more frequently malignant (adenocarcinoma) than the mixed odontogenic tumor. Being most common in the parotid and submaxillary gland, it occurs in the oral cavity. Ash[245] reports the following distribution in 683 cases: parotid, 503; submaxillary, 55; sublingual, 2; lip, 40; palate, 80; and tongue, 3. The tumor also occurs in the mandible, forming what appears in the x-ray picture as a cystic lesion.[197, 246] It may invade the bone from an adjacent neoplasm.[201] An excellent collective review of the subject, with an analysis of 50 cases, has recently been presented by Cheyne et al.[247] For differential diagnosis from inflammatory lesions, sialography has been recommended.[248]

Carcinoma

A long chapter could be written on the clinical appearance, complications and treatment of oral cancer, and many individual case reports and series of cases in special regions of the mouth and jaw may be found in the literature. Epidermoid carcinoma is more common than the transitional-cell lesion and the adenocarcinoma, which is found in the palate, cheek and lip.[249] Though the tumor is more common in the later part of life, no age is exempt. Two cases of malignant embryonal carcinoma have been reported — one in a child three years of age with a malignant epithelial tumor expanding the mandible and giving the appearance of an osteogenic sarcoma[250]; the other, in a nine-year-old child, probably was, like most of these tumors, formed from odontogenic epithelium in the jaw.[251]

Epidermoid carcinoma varies greatly in its appearance, origin, clinical course, histologic structure and complications. It may form an ulcerating, papillomatous exophytic, fungating, indurated lesion often associated with leukoplakia, and careful inspection and palpation are necessary in the examination. Woodbury[252] gives examples of cases that are constantly observed in the outpatient clinic of the Massachusetts General Hospital because of persistent sores, swellings or lymph-node enlargement that the patient regards as being due to dental conditions. Secondary involvement of the mandible occurs for various reasons. Buirge,[253] analyzing 71 cases, states that delay before diagnosis is made is the most frequent reason. Only 10 per cent of the patients were promptly referred by the dentist or physician to an appropriate source of therapy; in the other cases, there was an average delay of 8.4 months before definitive treatment was instituted.

More uncommon are other malignant tumors, which often give even the expert great difficulty in diagnosis. Fibrosarcoma and osteogenic sarcoma have already been discussed.

A Ewing tumor was reported as a possible primary lesion in a fifteen-year-old boy[201] complaining of a gradually increasing swelling of the body of the mandible, which responded dramatically to radiotherapy. In another case,[201] which showed striking radiologic changes in the mandible and involved the lateral wall of the left orbit and adjacent malar bone, a primary tumor involved the radius. Two cases were reported by Salman and Darlington.[254] One, in a seventeen-year-old boy, caused a large swelling extending from the premolar area to and including the anterior border of the ramus of the jaw; after resection of the jaw, multiple bony metastases formed. The other occurred in a thirty-six-year-old woman who, after pregnancy, noticed numbness in the right mandible and pain. After a tooth extraction, which brought no relief, metastases occurred.

Lymphosarcoma

Stout[255] discussed some of the reported cases and stated that 26 of 218 cases were primary in the mouth, pharynx or salivary glands. The gingiva

lesions may destroy the bone around or adjacent to the roots of teeth simulating periodontal abscesses.[183] In other cases ulceration[256] of the mucosa and the formation of fixed tissue masses on the gingiva and palate[197] are observed and are often of multiple occurrence.[257, 258] Frequently, adenopathy is present.[258] The tumor varies in malignancy and may be a localized process or distributed throughout the lymphatic tissue.[254] Extensive destruction of the mandible and maxilla has been observed,[257] and neurologic signs may be present, such as anesthesia of the lip.[258] A case of a girl three years old[201] illustrates the remarkable rapidity with which this tumor may grow, involving finally the entire left side of the face. Though these tumors generally respond well to roentgenotherapy, there was no response in the case described. A reticulum-cell sarcoma in a twenty-four-year-old man was reported by Goldman.[196] After being treated for Vincent's stomatitis, it was biopsied and diagnosed. It was treated successfully by irradiation (7200 r). Salman[254] reported 2 cases that ended fatally.

Multiple myeloma. A case of plasma-cell myeloma was diagnosed[201] by biopsy of a mass in the third molar region of an edentulous mandible. It was found to be part of a generalized process. Meloy and Gunter[259] reported another case of multiple myeloma, in which the largest and first lesion found produced pain and swelling in the mandible. On x-ray examination, a pathologic fracture of the mandible and multiple skeletal involvement were discovered.

Malignant melanoma. Melanoma may occur in the mouth, since melanophores and dopa-positive cells are numerous in the oral mucosa, especially among the dark-skinned races, but this tumor is extremely rare. Brown and Byars[260] give a good picture of a case occurring on the labial gingiva of a fifty-seven-year-old Negress. Arons[261] described a case occurring on the palate. Both patients died of metastases. Soderberg[262] reported 2 cases occurring in infants one month and two months old. Both were treated with radium, and both patients were free of disease five and six years later. A malignant melanoma of the floor of the mouth associated with an osteogenic sarcoma of the mandible was reported by Thoma[263] in a twenty-four-year-old man. In spite of resection of the mandible and electrocoagulation of the wound, the patient died of a malignant giant-cell tumor seven months later.

Tumor of the retinal anlage. This tumor, the first of its kind described, according to the reporter of the case,[264] occurred in a six-month-old female infant, forming a firm mass, 5 cm. in diameter, protruding from the palate and attached to the anterior part of the right maxilla. Though not malignant, it was radically removed and did not recur.

Metastatic carcinoma. Metastasis is not uncommon. The jaws show in most cases radiolucent areas in the x-ray films except in carcinoma from the prostate, which often causes osteoblastic activity. Adair and Herrmann[265] reported 5 cases of cancer of the breast with metastases involving the mandible. Pain or anesthesia and loosening of teeth are early symptoms. Salman and Darlington[254] reported 4 cases, 3 occurring in the mandible causing swelling or pain; the fourth was a hypernephroma that formed on the hard palate two years after a nephrectomy. An embryonal type of metastatic carcinoma from the testicle causing pain and localized in the third molar region of the maxilla was found in a sixty-four-year-old man by Cameron and Stetzer.[266]

The case reports of some of the malignant tumors reviewed prove that many physicians and dentists continue to be responsible for unpardonable delay in the treatment of these lesions by trying various types of medication and thus postponing the early diagnosis that is essential. In other cases a great deal of harm is done by ineffective treatment or treatment that is too conservative. Malignant tumors should be treated only by those trained in tumor surgery who are familiar with the surgical anatomy of the region involved and are able to perform procedures radical enough to increase the chance of a cure.

Conclusion

Oral surgery is a broad field offering a great variety of interests. In this review surgical diseases only have been covered. There are many other conditions that the oral surgeon deals with, which some classify as oral medicine. These are either local lesions treated by nonsurgical means or symptoms of some systemic disorder such as avitaminoses, blood dyscrasias, dermatoses, neuroses or general organic and skeletal diseases, which often require for their elimination close co-operation with the physician or specialists in other fields.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35191

PRESENTATION OF CASE

A thirty-eight-year-old French-American fish-cutter was admitted to the hospital because of jaundice.

The patient was perfectly well until four months before admission, when he had an episode of vomiting food recently eaten. This was followed by the onset of flatulence and a sensation of upper abdominal fullness and anorexia, which persisted until the time of entry. There were occasional cramps and increased urge to defecate. Three months prior to admission the urine became darker. Two weeks later it was "reddish" for a period of three days; this change was unassociated with pain, chills or fever. One week later jaundice and pruritus, associated with dark urine and clay-colored stools, developed. Two months before admission he noted the onset of a dull ache in the right upper quadrant, which became increasingly more severe, finally requiring an injection by his physician. Following this he was admitted to another hospital, where he remained for one month. During the first week in the hospital he was febrile, the temperature going as high as 102.5°F., but without chills or leukocytosis. Pain did not recur after the first hospital day, although jaundice persisted. Following a course of penicillin and aureomycin the temperature became normal, and the patient's appetite returned. A cephalin-flocculation test was negative. During the five weeks before entry he was on limited activity at home but despite a high-calorie, high-carbohydrate, high-protein, low-fat diet he became progressively worse. Jaundice persisted, flatulence, belching and "gas pains" became more severe, and it was noted that his weight, which before the onset of the illness had been 165 pounds, was now 130. During the week before admission he vomited just before each meal the food he had eaten at the previous meal. There was no history of hematemesis, although there were two questionable episodes of tarry stools three weeks before admission and on the day of admission, re-

spectively. Although jaundice had been constant, the color of the stools varied greatly from dark brown to light tan to clay.

Although his job was that of fish-cutter, he often supplemented his earnings by doing odd painting jobs and had been thus engaged, using a silver paint, shortly before the onset of the illness. There was no past history of jaundice or other serious disease, and he used alcohol only moderately.

Physical examination revealed a thin, jaundiced, middle-aged man lying comfortably in bed in no distress. No spider angiomas were noted, and the chest and heart were normal. The liver edge, on inspiration, was palpable 2 cm. below the costal margin and was smooth and nontender. No other organs or masses were felt, and there was no tenderness.

The temperature was 100°F., the pulse 80, and the respirations 15. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 4,900,000, with a hemoglobin of 15 gm., and a white-cell count of 8400, with 54 per cent neutrophils. The total protein was 7.25 gm. per 100 cc., with 5.02 gm. of albumin and 2.23 gm. of globulin (albumin-globulin ratio of 2.3). The cholesterol was 320 mg. and the cholesterol esters 216 mg. per 100 cc. The van den Bergh test was 8.4 mg. per 100 cc. direct and 10.6 mg. indirect. The cephalin-flocculation test was negative in twenty-four and forty-eight hours; the thymol turbidity was 1.0 units, the prothrombin time 17 seconds (control, 15 seconds), and the alkaline phosphatase 9.3 units. The urine gave a +++ test for bile on repeated examinations. The stools varied in color from dark brown through yellow brown to metallic gray and, with a single exception, gave ++ or +++ guaiac tests.

In the hospital the patient seemed somewhat improved and ate extremely well, complaining that the diet given him was inadequate. On the sixth hospital day the urinary urobilinogen was 3.7 Ehrlich units. The serum amylase was 123 units and lipase 3.4 units per cubic centimeter. The fasting blood sugar was 103 mg. per 100 cc. A plain film of the abdomen was negative for gallstones and showed no enlargement of the liver or spleen. A roentgenogram of the chest was within normal limits. A gastrointestinal series revealed no abnormality in the esophagus, stomach or duodenal cap. There was slight narrowing of the duodenum in the post-bulbar region, but this was not constant. The remainder of the duodenum showed no defect or displacement, and no stones were identified in the region of the common duct.

On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. Earle M. Chapman: When one tries to reconstruct the story of jaundice the record says, "the jaundice was constant." I cannot tell whether the jaundice was of three weeks' duration or longer. I suppose it persisted throughout his illness.

Dr. Alfred Kranes: The jaundice was constant but fluctuated in degree, not only clinically but also by chemical tests. When the patient was discharged from the other hospital the icteric index was considerably below that of admission. The jaundice never completely disappeared.

Dr. Chapman: That is helpful. The record states that the patient used alcohol only moderately. Did you decide that it was moderate?

Dr. Kranes: I did not know about that.

Dr. Chapman: Was his temperature rectal or by mouth? I assume it was by mouth since it is not stated. If so, he had a fever.

Dr. Kranes: He had no fever in this hospital except for one period of twenty-four hours.

Dr. Chapman: I think we had better see the x-ray films at this point. The record states that they were normal except for what is described as slight narrowing of the duodenum in the post-bulbar region.

Dr. Stanley M. Wyman: The films of the chest are not remarkable. The liver shadow as described appears within the limits of normal. There is no evidence of intrinsic disease in the stomach. The narrowing of the post-bulbar region of the duodenum is seen at this point, and it appears on the spot films. It does seem to change somewhat in caliber.

Dr. Chapman: Compression from something external?

Dr. Wyman: Pressure from something extrinsic. The mucosal pattern is perfectly normal in the entire area. There is no evidence of convergence of folds. It looks as if something is pressing on the distal portion of the duodenal cap, causing a narrowing rather than something intrinsic in the duodenum. There is another finding of considerable value, and that is what I believe to be compression of the second portion of the duodenum on its medial aspect about at the junction of the middle and distal thirds over an area measuring 2.5 cm. in length. This is also seen on this spot film, in which there is a filling defect at this point. It is not reproduced on all the films.

Dr. Chapman: That lies in the region of the head of the pancreas anatomically.

Dr. Wyman: Yes. Although it is well visualized on only two or three films, and not on all films, the filling defect is a valid finding.

Dr. Chapman: I think it is more significant than I was led to believe from reading the record. There is more mischief in this area from looking at the film than I thought from the description. What was found at operation is what they are asking me. I will start by saying that I have no idea really. It is a difficult diagnostic problem. Since this man was a fish-cutter, we have to consider

Weil's disease. It probably is a "red herring." Davidson* reported Weil's disease in fish-cutters in Scotland, who acquired it in their occupation. This man did not have an acute disease and was almost afebrile, so I think we can exclude Weil's disease. However, the illness started with dark urine.

DR. KRANES: The dark urine noted the week before the jaundice was hematuria. It had a good many red cells in it.

DR. CHAPMAN: That is interesting. The record said "dark" urine; it did not say "bloody" urine.

DR. KRANES: I did not see it. His family said that microscopically it was full of red cells.

DR. CHAPMAN: I thought of the possibility of Weil's disease. The patient was a fish-cutter, and we have seen the disease among people with that occupation in Boston. Yet this seemed like a chronic disease. If it was a complication of Weil's disease we ought to find something like abscess in the region of the head of the pancreas. This bothered me a little, but I decided to exclude it because the progress of the illness did not seem to fit the diagnosis and someone should have made a diagnosis of Weil's disease. But there it is — he was a fish-cutter, with a febrile illness to start with. Why did it take so long? I did not think of it last night when I first read the record, but now that I have seen the films I am thinking of the possibility of abscess. I have to change my thinking of 11:30 last night.

The laboratory evidence is confusing, but from it one gathers that there is no good evidence on which to base the diagnosis of intrinsic liver disease. I do not see how we can support cirrhosis or infectious hepatitis. All the laboratory changes are consistent with the intermittent type of obstruction to the outflow of bile. The clinical description Dr. Kranes gave us and the laboratory changes all fit together.

We are faced with the question of what would lead to an intermittent obstruction in the region of the head of the pancreas. What lesion would fit with the x-ray evidence? Of course the commonest thing in this location, even though thirty-eight years of age is a little young, is carcinoma of the head of the pancreas. We know that carcinoma in the head of the pancreas can erode the ampulla of Vater and lead to blood in the stools, and it can lead to intermittent obstruction and cause the type of distortion seen in the x-ray film. That is the likeliest possibility, but there is one thing strikingly against the diagnosis of cancer. I cannot believe that a man who had cancer and who died of it, let us say, would complain that the diet in the hospital was inadequate and want more food. That is a clinical fact against carcinoma of the head of the pancreas. That is the one statement that I underlined as being against that diagnosis.

Could he have had a stone, a so-called silent stone, in the head of the pancreas? A large nonopaque stone does not cause a shadow and could have bored in there and got mixed in with the pancreatic duct and eroded the whole area and caused mischief.

If we go back to the beginning of the history, he had occasional cramps and increased urge to defecate when the illness started. If we try to reconstruct the events from the beginning of the illness we have to consider silent stone in the head of the pancreas, not reflected here in the x-ray films, and then consider inflammatory reaction around it. There must have been considerable inflammatory reaction around this area whatever it is, because the serum amylase was high (123 units), which is evidence of destruction of the pancreas. The upper limit of normal is 40 units. I might say in passing that jaundice has been described as coming on after penicillin and also described after pentothal anesthesia. He did not have any such things injected into him, did he, Dr. Kranes?

DR. KRANES: Penicillin was given by the family physician after the patient had become jaundiced because he was running a septic fever.

DR. CHAPMAN: But he had had no operative procedure, before the onset of the illness. I wondered if it might be related to an infected syringe or anything of that sort. There was nothing of that nature antecedent that you know of?

DR. KRANES: No.

DR. CHAPMAN: Was this, then, a stone, a tumor or an inflammatory mass? I am beginning to change my mind. Last night I was all for cancer of the head of the pancreas or ampulla of Vater. Having seen the films and reconstructed the story, however, I am now thinking that this mass was inflammatory and that is about as far as I can go. I do not see how an area of constriction across this region such as Dr. Wyman described can come from a vascular structure. I had thought of aneurysm of the abdominal aorta, but that does not fit this, does it?

DR. WYMAN: No, but it fits with dilated common duct pressing on the duodenum.

DR. CHAPMAN: I cannot do any better than this. We might give someone else in the audience a chance.

DR. JACOB LERMAN: What did the X-ray Department think it was?

DR. BENJAMIN CASTLEMAN: They thought it was inflammatory.

DR. CHAPMAN: I did not mention retroperitoneal lymphoma. I considered the possibility of a tumor of the lymphoma series involving the head of the pancreas and pressing on the duodenum.

DR. HOWARD B. SPRAGUE: Could it have started with pancreatitis?

*Davidson, L. S. P., and Smith, J. Weil's disease in fishworkers: clinical, chemical and bacteriological study of 40 cases. *Quart. J. Med.* 5:263-286, 1936.

Dr. Chapman: An inflammatory mass subsequent to ordinary pancreatitis? Yes, that is perfectly possible. My first choice is an inflammatory mass, with pancreatic destruction. That fits the laboratory evidence best, and what lies behind that remains to be seen.

Dr. Wyman: There is a suggestion that this is well localized, so that I should place more emphasis on common-duct stone with secondary dilatation of the common duct or a tumor of the ampulla of Vater or the distal end of the common duct. However, a carcinoma of the pancreas or, I suppose, an inflammatory mass could look exactly the same.

Dr. Castleman: Have you any comment, Dr. Boyd?

Dr. William Boyd (Toronto): I think pancreatitis of some type might be all right.

Dr. Lyman Duff (Montreal): The possibility of pancreatic cyst might be suggested; that is no more impossible than any of the other suggestions made.

Dr. Kranes: I saw this patient on only one occasion about one month after he became ill in the other hospital. At that time he was on the mend, the jaundice diminishing, his appetite, which had previously been very poor, had increased enormously, and in general he was a great deal better. The history at the time — jaundice, nausea and fever, followed by the subsidence of the jaundice and the return of the appetite — was fairly characteristic of acute hepatitis. I might say in further support of that diagnosis that he was rather tender in the right upper quadrant. That is not brought out well in the history. The only thing that disturbed us was the fact that the fever occurred about two or three weeks after the onset of the jaundice rather than preceding the jaundice, and the laboratory tests were those of obstructive jaundice. Since he was improving it was decided to let him go home and see if he continued to improve. As the history brings out, although the appetite remained good he continued to lose weight, his jaundice grew more intense and repeated cephalin-flocculation tests done during this period were negative. So he was readmitted to the hospital with a diagnosis of obstructive jaundice. When he arrived on the ward everyone who saw him from students to house officers and visiting physicians all thought he had hepatitis until the results from the laboratory work were returned and the impressions were changed.

Clinical Diagnosis

Infectious hepatitis?
Obstructive jaundice?

Dr. Chapman's Diagnosis

Inflammatory mass in region of head of pancreas.

Anatomical Diagnosis

Adenocarcinoma (low grade) of ampulla of Vater.

Pathological Discussion

Dr. Castleman: The operation on the tenth day was an aspiration of the liver, which showed evidence of biliary obstruction. The bile ducts were all distended with bile. There was no doubt of an obstructive jaundice, and with that diagnosis Dr. Linton operated. He found a large, distended gall bladder; the head of the pancreas felt pretty hard, but a rush frozen section on a biopsy showed normal pancreas. The common duct was markedly thickened and dilated, probably two or three times the normal size; this was strong evidence that there was an obstruction at the ampulla. The duodenum was therefore opened, disclosing a papillary lesion surrounding the papilla of Vater. A Whipple operation, which consisted in removing the head of the pancreas and duodenum and anastomosing the end of the common duct into the jejunum, was then performed.

The specimen we received showed a papillary tumor measuring 4 cm. in diameter probably arising in the duodenum, completely surrounding the ampulla and producing complete obstruction. The center of the tumor was at the ampulla. Histologically this was a slowly growing adenocarcinoma with very little invasion. We found one spot where it had gone beyond the muscularis mucosa, but there was no invasion of the pancreas at all.

Following operation the patient developed a localized abscess which was drained, and he is apparently doing well. A dozen regional lymph nodes were examined, and they were all normal. I am quite certain that there are no metastases.

CASE 35192

Presentation of Case

First admission. A seventy-five-year-old man was admitted to the hospital complaining of occasional abdominal pain and gaseous eructations.

Ten to twelve months previously he began having intermittent bouts of aching right-lower-quadrant pain, usually occurring at night. Six months before admission these pains became sharp and crampy and were severe enough to interfere with his sleep. They usually lasted two or three hours and were relieved somewhat by enemas. He had always been somewhat constipated, and he noted no change in the character of the stools. A system review was negative except for occasional slight ankle edema and some urinary frequency. Approximately one month before entry a complete checkup, including a gall-bladder and large-bowel x-ray series, was reported as negative in an outside hospital. A pulsating mass in the left upper

quadrant was found, and he was referred to this hospital.

Physical examination was entirely negative except for a pulsating, 10-cm., rounded mass in the left upper quadrant, presenting just below the costal margin.

The temperature was 98.6°F., the pulse 60, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

Laboratory studies showed a cloudy urine, with a specific gravity of 1.012, with 4 white blood cells per high-power field in the spun sediment. The hemoglobin was 11.8 gm.

Chest x-ray films disclosed enlargement of the heart in the region of the left ventricle and a tortuous, elongated aorta. Plain films of the abdomen demonstrated a smooth mass, extending from the level of the twelfth thoracic vertebra about 9.5 cm. to the left of the midline. There was some calcification about the periphery of the mass. The left kidney was possibly displaced slightly laterally. The right kidney was not remarkable. On the third hospital day wiring of the abdominal aneurysm was done by means of a trocar needle inserted through the back. He was discharged one week later.

Final admission (six months later). The patient continued to have daily attacks of severe abdominal pain, which was sometimes burning, sometimes sharp and crampy and sometimes aching. He gradually developed increasing constipation, progressing to almost complete obstipation, and had episodes of vomiting two or three times a week. His appetite gradually diminished, and he lost considerable weight.

Physical examination showed slight icterus, a hard, irregular liver edge, extending four finger-breadths below the costal margin, and an 8-cm. mass in the right lower quadrant. There was, again, the 10-cm., pulsating mass in the left upper quadrant. The abdomen was distended and tympanitic, with high-pitched peristaltic gurgles. There was ++ edema of the ankles. The patient became increasingly jaundiced and more listless and died.

Differential Diagnosis

Dr. Richard J. Clark: We are given the history of a seventy-five-year-old man whose symptoms started out approximately eighteen months prior to his final admission to the hospital. He had crampy abdominal pains all through this period, which were apparently somewhat related to constipation — not too definitely at first, but quite definitely later on. Various studies were made, including gall-bladder x-ray films and a barium enema, which were said to have been negative at that time. A pulsating mass was found in the left upper quadrant. He came into the hospital, and the diagnosis of aneurysm was apparently made. We are told that this was wired. We have to be suspicious when given such a flat-footed diagnosis, but there seems little reason to doubt that the patient had an abdominal aneurysm. In spite of the wiring of this aneurysm, he had no relief of pain, and he went on developing increasing constipation, weight loss, anorexia and finally vomiting. He returned to the hospital following a progressively downhill course and on the second entry presented a mass in the right lower quadrant and a liver that had become enlarged and nodular. He died without any sudden dramatic event.

The problems presented here are twofold: the nature of the pulsating mass in the left upper quadrant and its relation to symptoms; and the nature of the mass in the right lower quadrant and its association with the abnormal liver and the course of events. May we see the x-ray films?

Dr. Stanley M. Wyman: The films of the chest are not remarkable except to demonstrate a heart that is prominent in the region of the left ventricle and a somewhat tortuous thoracic aorta. The films of the abdomen show the wired aneurysm, and the soft-tissue mass extending peripherally to the right is well seen. The lateral view discloses calcification in the walls of the aneurysm itself. The only other thing of particular note is the increase in the size of the liver from the first admission to the second, when it appears to be definitely larger.

Dr. Clark: Is there any appreciable change in the appearance of the lesion?

Dr. Wyman: Both these films are taken after the wiring, about six months apart, and there is no definite change that I can see.

Dr. Clark: Can you follow the course of the abdominal aorta at all?

Dr. Wyman: The calcification here lies in the aneurysm. It is impossible to follow it with accuracy, but it seems to extend in this fashion. Down below, it is readily seen where it comes out to more or less normal caliber at the level of the fourth lumbar interspace. The aneurysm itself lies apparently between the twelfth thoracic and the fourth lumbar vertebra.

Dr. Clark: Dr. Wyman has been kind to us in granting that this is an aneurysm. He has left relatively little doubt about that particular point.

This man obviously had arteriosclerosis. We have no record over the course of time of his having had hypertension. Possibly he had it at some time in the past, but he was not in congestive failure. I see no definite indication for making a diagnosis of hypertensive heart disease. Lacking evidence for any other etiologic factor, we may reasonably assume that this patient had an arteriosclerotic form of heart disease, with arteriosclerosis of the aorta. Certainly from the descriptions given we may assume that he also had an abdominal aneurysm. The question arises just where the aneurysm was located. The three commonest locations are the abdominal aorta, the splenic artery and the hepatic artery. From the description we might have suspected origin

from the splenic artery, but it seems quite definite from the size of the aneurysm and the x-ray appearance in relation to the abdominal aorta that the aneurysm arose from the aorta. The next question is, What was the etiology of the aneurysm? While many aneurysms are syphilitic in origin, those of the thoracic aorta are more apt to be syphilitic, whereas I believe it has been shown in this laboratory that the majority of intra-abdominal aneurysms are arteriosclerotic. Was a serologic test done?

DR. TRACY B. MALLORY: Yes, and it was negative.

DR. CLARK: That would be further evidence that this probably was an arteriosclerotic aneurysm of the abdominal aorta. What relation did this aneurysm have to the patient's presenting symptoms? Aneurysms by themselves do not ordinarily produce pain. Pain and other symptoms of aneurysm are almost entirely caused by their effect upon adjacent structures, from erosion, pressure and the like. Symptoms from aneurysm in the abdomen are apt to be notably absent because there is plenty of room for expansion, and pressure symptoms are less likely to occur. I toyed with the thought of involvement of the ostia of various branches of the aorta leading to the mesentery. Could this symptomatology have been related to what has been described as abdominal angina secondary to arteriosclerosis of abdominal vessels? It seems to me that in view of subsequent evidence there is no need to bring in any such supposition. I do not believe that the aneurysm had any important relation either to the patient's death or to the patient's symptoms, although symptoms of nausea, anorexia and so forth have been attributed to such lesions.

On the final entry we are given very few facts and almost no specific data on which to confirm or establish a diagnosis. Apparently no x-ray studies were done and no laboratory data are at hand. We do have the appearance of a tumor that had arisen in the right lower quadrant, and we have evidence of involvement of the liver. There are no data on which to substantiate a diagnosis of infection: nothing is said about tenderness in the mass or in the liver; there is no record of fever or leukocytosis. This leads us almost certainly to a neoplastic lesion. We might go through all the neoplasms in the lower abdomen that could metastasize to the liver, but in view of the rather definite symptoms of increasing constipation, weight loss and so forth, without further ado we might just as well make the assumption that this patient had carcinoma of the colon, most likely in the region of the cecum, with metastases to the liver, and that he probably died as a result of this. The lesion was likely present but undiscovered at the time of the first x-ray examination. I cannot reasonably relate the aneurysm with the right-lower-quadrant mass or the liver. That leaves me with a diagnosis of arteriosclerotic heart disease, arteriosclerotic aorta, with an arteriosclerotic aneurysm of the abdominal aorta together with carcinoma of the colon and metastases to the liver.

CLINICAL DIAGNOSES

Carcinoma of colon, with metastases to liver.
Abdominal aneurysm.
Arteriosclerosis.

DR. CLARK'S DIAGNOSES

Carcinoma of colon, with metastases to liver.
Arteriosclerotic aneurysm of abdominal aorta.

ANATOMICAL DIAGNOSES

Carcinoma of ascending colon, with metastases to liver, regional lymph nodes, lungs and kidney.
Arteriosclerotic aneurysm of abdominal aorta, wired.

Arteriosclerosis, generalized, severe.
Bronchopneumonia.
Pulmonary emboli, small.
Thrombosis, periprostatic plexus of veins.

PATHOLOGICAL DISCUSSION

DR. ROBERT R. LINTON: I would like to compliment Dr. Clark on his presentation of this case. He has described everything that I know about it. I will show some color slides, which will confirm his diagnosis. This first slide is a view of the abdomen when it was opened at autopsy. It shows a huge liver. Here is the left lobe with the metastatic nodules in the liver itself. There is nothing else of note in that view. This is the cut section of the liver. Much of the liver tissue was replaced or pushed aside by this tremendous infiltration of metastatic disease. The next slide shows the aorta and the aneurysm, the abdominal aneurysm, which has been wired. The next view shows the aorta when it has been opened. We have been unable to obtain many such specimens after wiring. There is a dark area that contains many of the loops of wire and

fresh blood clot, which is post-mortem clot. This portion out here is a gristle-like, partially organized thrombus. The wiring did what it was supposed to do — that is, it strengthened the wall of the aneurysmal sac so that it did not perforate and through it a channel led whereby blood could flow freely to the lower part of the body in spite of numerous coils of steel wire. The next is a closer view, showing the channel through which the blood flowed.

I became interested in the wiring of aneurysms because of the fact that we have a certain number of arteriosclerotic aneurysms that are the cause of a patient's death. Having watched a number of them perforate or rupture, and watched the patient suddenly expire, it seemed that one was justified to try almost anything to save their lives. Wiring of aneurysms dates back many years. I do not know who was the first courageous surgeon to attempt it, but it fell into disrepute chiefly because surgeons did not have the proper type of wire to use. The difficulty with the wire used formerly was that it was too stiff and rigid and followed the path of least resistance and ended up where one did not want it to go. The wire I have used is stainless steel, No. 30 gauge, and very flexible so that it coils around without traveling up and down the aorta.

We must rely on preoperative x-ray studies to determine the cause of many patients' symptoms. If an abdominal arteriosclerotic aneurysm is found on examination I would like to warn that very often it is nothing but a red herring, and the cause of the symptoms is some other disease. In the case under discussion I unfortunately relied on a single x-ray examination taken at another hospital. The patient had had a barium enema and a gastrointestinal series, and the x-ray studies were reported as negative. I took that to be true and, as a result, decided to wire this aneurysm from a lumbar approach, which necessitates only a nick of the skin to insert the wiring trocar, and with this approach one can wire the abdominal aorta just as well from behind as in front. I did the wiring last June, thinking that the aneurysm was the cause of the symptoms, as did his local physician. It was not until the patient developed a mass in the right lower quadrant that we decided to reinvestigate his gastrointestinal tract, and on a more careful search we found a lesion in the cecum, which Dr. Wyman also demonstrated by roentgenologic examination a short time before the patient's death. The lesson I learned from this case was: not to rely on a single gastrointestinal series in a patient who has symptoms that do not seem typical of an abdominal aneurysm. I thought I was very smart a little while later because I had another patient come to me the latter part of last year. This patient was sixty-three years old; he was referred to me because of a mass in the abdomen, which obviously was the same kind of lesion, an arteriosclerotic abdominal aneurysm, which one can see in the x-ray films has been wired. His symptoms were those of obstruction — for six years he had had discomfort after eating heavy, fatty meals. The aneurysm was noted about one month before he came to me and during the last two weeks had increased in size. It seemed to me that his symptomatology suggested something wrong with his gastrointestinal tract, so I had a gastrointestinal series performed. The report came back that this mass was a prepyloric ulcer on the lesser curvature. Do you agree, Dr. Wyman?

DR. STANLEY M. WYMAN: It looks like it.

DR. LINTON: I believe there was no question of correctness of this diagnosis since we all thought this man's symptoms were due to the prepyloric ulcer, so I transferred him to an internist for treatment of the prepyloric ulcer and determined to forget about the aneurysm for the present. A few days after the internist saw him the patient began to complain of terrific pain in the back, radiating to the groins. The aneurysm increased in size, and it was obvious that it was beginning to rupture and for that reason we did an emergency laparotomy and wired the aneurysm. Since then the pain in the groin and back disappeared. Here was a man with two lesions — the one that brought him to the hospital was the abdominal aneurysm, although the history was that of prepyloric ulcer. I have another that I would like to show. This is a sixty-five-year-old man who came to me in December. The chief complaint was indigestion. I took one look at him and said, "This man is not coming to me because of his aneurysm; he is coming to me because he has something else wrong with him." Examination revealed a large arteriosclerotic abdominal aneurysm. It was my opinion, however, that the man had a gastric lesion, and I thought that it probably was malignant. I referred him to the hospital, and the first thing done was a gastrointestinal series, which was reported negative. Because the pain was atypical for aneurysm, we thought of doing a Graham test, which showed a

number of calculi in the gall bladder. We finally decided to operate on him to take out the gall bladder and wire the aneurysm at the same time. To my consternation, when I opened his abdomen I found that he had a huge carcinoma of the stomach involving the fundus, which necessitated a total gastrectomy. So I ended up by doing that and let the aneurysm alone. I did not think it was justifiable to do both procedures at the same time. Another patient, referred to me by Dr. Arthur W. Allen, said that he was lying in bed one night, reading a book, and he noticed that it jumped up and down with every heart beat, and he became interested and found that he had an aneurysm. He had no symptoms whatever except the mass that kept bouncing up and down. In his case the aneurysm was successfully wired. Even after a most careful x-ray workup I still think that if one is going to wire an abdominal aneurysm (and I believe they should be wired because they probably will rupture sooner or later) it should be done through an abdominal exploratory incision rather than through the back with a small incision. In that way one can pick up a certain number of these patients who have other diseases and correct them and perhaps later on take care of the aneurysm.

Dr. Clark: Was the original lesion in the cecum?

Dr. Mallory: It was in the ascending colon, just above the cecum — there were extensive metastases to the liver and generalized, diffuse arteriosclerosis.

Dr. Clark: Did the heart show anything more?

Dr. Mallory: Nothing except diffuse coronary sclerosis without infarction.

Dr. Linton: In defense of the original barium-enema examination, I do not believe anyone would have found the tumor at the time it was done. Even before death the lesion was not too obvious or large at autopsy.

Dr. Wyman: In defense of the first examiner who saw the patient, the lesion must have been small because when I saw the films seven months later, before death, it was only 5 cm. in length.

Dr. Linton: I even shudder to think that I might have missed it had I done an exploratory laparotomy.

Dr. Clark: How much hazard is there involved in doing a wiring of this sort — do you have any way of knowing what the results are? Have you followed enough patients over a period to know how much good is accomplished?

Dr. Linton: I think that is hard to answer. I had a long letter from Dr. Cole, of England, who developed a wiring apparatus, and he said that he had spent his life trying to determine whether wiring of aneurysms prolonged life, and he was going to die without accomplishing it. It is difficult to say. There is a man from Atlanta, Georgia, in the hospital now with an abdominal aneurysm. The aneurysm began to leak while he was motoring through Connecticut. He was rushed to a hospital and referred here for treatment. I think, without question, that he would not have lived if the aneurysm had not been wired at that time. The thing that encourages me most to continue this treatment is that the autopsy in the case under discussion today showed that one can strengthen the wall and prevent it from perforating by this method.

Dr. Clark: What is the risk of the procedure?

Dr. Linton: The mortality is zero. I have done about 15 or 20 operations, which brings it down to a fairly reasonable risk. However, I am sure I will never do another through the back, no matter how sure we are by preoperative studies that that is the only trouble the patient has.

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ALL ROADS LEAD TO WORCESTER

The one hundred and sixty-eighth annual meeting of the Massachusetts Medical Society will be held at the Worcester Memorial Auditorium on May 24, 25 and 26. This will be the first meeting away from Boston in a decade, the last out-of-town meeting having been held in Worcester in 1939.

The quality of the meetings of the Society has improved steadily since the war, and their popularity has increased out of all proportion to the increase in the Society's membership. In 1947, 1521 fellows and guests registered their attendance, and in 1948, 2436. While a meeting outside Boston does not ordinarily attract the numbers that a meeting in the more densely populated section of the state can draw, every effort is being made to secure an especially large attendance this year.

As usual, the Council of the Society will meet on Monday evening, the day before the sessions begin, at the Hotel Sheraton. On the following morning, at 8:55, the first general session will convene in the Little Theater of the Memorial Auditorium. General sessions will continue to be held each morning and afternoon through Thursday, May 26.

The annual meeting of the Society will take place in the Memorial Auditorium at 11:00 on Tuesday morning, May 24. The annual oration, "Some Responsibilities of Medical Education," by Dr. C. Sidney Burwell, dean of the Harvard Medical School, will immediately follow. At the close of the oration the annual luncheon will be served. The Worcester District Medical Society has invited all members of the Massachusetts Medical Society to "Worcester Hofbrau Night" that evening, in the ballroom of the Sheraton. As if any inducements to attend were necessary, free entertainment will be furnished, and free beer will be served.

The Shattuck Lecture, always an event of great interest, will be delivered on Wednesday morning at 11:05 by Dr. Paul D. White, clinical professor of medicine at the Harvard Medical School, consultant in medicine at the Massachusetts General Hospital, and executive director of the National Advisory Heart Council. His subject is "La médecine du coeur."

The high point of the meeting will be the annual dinner on the evening of May 25, to which ladies may be invited. Tickets for the dinner, the fellows are warned, MUST be procured in advance. The speaker of the evening will be Roscoe Pound, LL.D., University Professor Emeritus, Harvard University, and former dean of the Harvard Law School, on the subject, "The Professions in the Society of Today."

The usual section meetings and luncheon will round out the program, and as usual the scientific and technical exhibits and the exhibition of works of art by members of the Massachusetts Physicians' Art Association will be well worth visiting.

This year, also, the Woman's Auxiliary will be on the scene as a full-fledged, functioning organ-

ization, with all but one or two districts participating. With a year's experience since its organizational meeting, it will hold its first annual meeting on May 24 at the Worcester Woman's Club.

All roads lead to Worcester; come one, come all!

ANTIBIOTIC THERAPY OF TYPHOID FEVER

Typhoid fever is one of the few acute bacterial infections in which modern chemotherapy has not yielded very brilliant results. It is generally agreed that the sulfonamide drugs have no effect whatever on the course of this disease, although they exert a definite bacteriostatic effect on the causative organisms in vitro. There have, however, been some conflicting claims concerning the effects of the combined use of penicillin and sulfonamides, and there are indications that some of the newer antibiotics may be beneficial. Since this disease, because of its possible severity in the individual patient and because of its public-health aspects, may assume importance out of proportion to its frequency, it may be of interest to review some of the recent reports on the effects of chemotherapy.

It is now generally appreciated that many gram-negative bacilli and particularly the typhoid bacilli are not totally resistant to the action of penicillin. They are essentially like the less sensitive strains of staphylococci in that they require relatively high concentrations to inhibit their growth. Evans[1] found that most strains of this organism were inhibited by 5 to 10 units of penicillin per cubic centimeter, and Welch and Randall[2] reported that all but 1 of 29 strains of typhoid bacilli tested were inhibited by 12 units or less of penicillin G, and all 29 were inhibited by 6 units of penicillin X.

In vitro studies carried out by Bigger[3] showed that penicillin in concentrations up to 8 units per cubic centimeter reduced but did not prevent the growth of *Eberthella typhosa* in broth. Sulfathiazole in concentrations up to 10 mg. per 100 cc. inhibited the multiplication of these organisms, but a bactericidal effect was obtained only when small numbers of bacteria were exposed. The combination of penicillin and sulfathiazole, however, had a pronounced bactericidal effect. Thus, a concentration of 4 units of penicillin per cubic centimeter and 10 mg. of sulfathiazole per 100 cc. sterilized a culture inoculated with 70,000 typhoid bacilli per cubic centimeter, and 1 unit of penicillin with the same amount of sulfathiazole sterilized a culture inoculated with 7000 organisms per cubic centimeter. On the basis of his findings, Bigger suggested a tentative therapeutic regime for the treatment of typhoid fever. This consisted of full doses of sulfathiazole in addition to penicillin in doses of 2,500,000 to 3,000,000 units per day by continuous drip for five to seven days. This dosage would be expected to maintain a concentration of 2 units of penicillin per cubic centimeter of blood. Both these agents would be given again if typhoid organisms reappeared in blood or stools.

Following this suggestion McSweeney[4] treated a series of 6 severe cases. One of his patients who received doses of penicillin appropriate for ordinary staphylococcal infections showed no appreciable effect on the pyrexia or blood cultures, although the toxemia was much lessened. The other 5 patients were treated intensively with penicillin and sulfathiazole and received two courses, each comprising 10,000,000 units of penicillin and 34 gm. of sulfathiazole in four days. Speedy disappearance of toxemia, subsidence of pyrexia and disappearance of organisms from the blood, feces and urine followed the end of the second course in 4 of these 5 patients. McSweeney regarded the clinical effects observed as confirming the laboratory findings of Bigger.

In a later and somewhat more extensive study, Bevan and his co-workers[5] treated 39 patients with penicillin and sulfathiazole in doses comparable to those used by McSweeney. The cases all occurred in a single outbreak. These workers did not observe the speedy disappearance of toxemia and subsidence of fever described by McSweeney. In the cases treated by this method, there was no evidence of any appreciable clinical effect of the drug treatment when compared with comparable cases in which the patients did not receive this therapy. Furthermore, a considerable proportion of the patients yielded positive blood cultures shortly after completion of the course of penicillin and sulfathiazole, and fecal excretion of typhoid bacilli during convalescence was not shorter in the treated

group than in the controls. The typhoid strain responsible for the outbreak was no more resistant to the action of penicillin and sulfathiazole than other strains with which it was compared in vitro. Bevan and his co-workers therefore considered it necessary to warn against the indiscriminate use of penicillin and sulfathiazole in the treatment of typhoid fever.

McSweeney was sufficiently impressed with the bacteriologic effects of the penicillin and sulfathiazole therapy in his cases to suggest that the same regime be tried in attempts to clear up typhoid carriers. Comerford,[6] following this lead, used both sulfathiazole and penicillin on 2 known carriers who regularly excreted typhoid bacilli even after cholecystectomy. He used 2 gm. of sulfathiazole followed by 1 gm. every 4 hours by mouth, and 500,000 units of penicillin intramuscularly at the same interval. This was continued for seven or eight days, and in both patients the stool cultures remained free of typhoid bacilli for a follow-up period of about four months. In another study, however, Fry and his associates[7] used the same regime in 17 chronic fecal carriers. There were only 3 apparent successes. In 2 of the cases in which the usual doses had failed, doses of 40,000,000 units and 12 gm. of sulfathiazole per day were given on three occasions and proved unsuccessful. These workers concluded that the therapeutic results of the penicillin and sulfathiazole treatment in typhoid carriers were not encouraging.

The introduction of streptomycin raised new hopes for effective therapy in typhoid fever because of the susceptibility of the organisms to this antibiotic in vitro. Reimann, Elias and Price[8] treated 5 patients with severe typhoid fever, and on doses of 1 to 4 gm. per day intravenously or intramuscularly obtained levels of streptomycin in the blood and urine that were more than sufficient to kill the organisms in vitro. Small quantities of the antibiotic were also excreted in the feces. Both parenteral and oral administration of streptomycin was considered desirable, the former to control the bacteremia and bacilluria and the latter to sterilize the feces and prevent reinfection and the carrier state. There was no evidence of the development of increased resistance during exposure of the organisms to streptomycin in the body. However, only 3 of the 5 patients recovered, and, in addition, bacillemia and positive stool cultures persisted in some cases in spite of the exposure of the organisms to concentrations of streptomycin greater than that required to kill the organisms in vitro.

Since this study of Reimann and his associates, it has been amply demonstrated that streptomycin has little if any favorable effect on the clinical and bacteriologic course of typhoid fever. The 169 cases collected by Keefer and Hewitt[9] seemed to bear this out.

Of interest is the failure in most cases of typhoid fever to demonstrate the development of resistance in organisms that persist in the blood and stools during treatment with streptomycin. Comparable observations have been made by Hall and Spink[10] in cases of brucellosis. Such findings suggest either the failure of the antibiotic to obtain access to the bacteria or possibly a difference in the genetic constitution of these organisms that affects the mutations concerned in the development of streptomycin-resistant flora. Of additional interest is the demonstration of "hormesis" (an increase in the mortality rate) among mice infected with typhoid bacilli and treated with subeffective concentrations of either penicillin[11] or streptomycin.[12] The immunity that followed the typhoid infection in the streptomycin-treated mice that recovered suggested that when the small doses of drug were used, there was actually multiplication of the organisms in vivo.

It is natural that new antibiotics that are relatively nontoxic and have a definite effect on gram-negative bacilli in vitro and in experimental infections should receive a clinical trial in the treatment of typhoid fever. Preliminary trials of two such antibiotics have appeared recently. Ten cases of typhoid fever were treated with chloromycetin[13] in Kuala Lumpur during the course of clinical trials with this agent in scrub typhus. The course of the typhoid fever was markedly shortened in comparison with that in untreated cases, and the febrile stage of the illness was terminated in an average of three and a half days after treatment was begun. These patients were treated orally with an initial dose of 50 mg. per kilogram of body weight,

followed by 0.25 gm. every three or four hours and smaller doses after the temperature had been reduced. Concentrations of chloromycetin that were many times the bacteriostatic levels for the organisms were obtained in the serum.

Even in this small group of chloromycetin-treated cases, however, some of the reported observations indicate that the beneficial results were far from optimal. Positive stools were obtained in 2 patients during convalescence; 2 other patients had relapses of fever with positive blood cultures after being afebrile for ten to sixteen days; 1 patient had an intestinal perforation two days after the temperature had returned to normal, and another had a large hemorrhage from the bowel after being afebrile for four days.

Aureomycin is the most recent antibiotic to receive a trial in typhoid fever. This agent is effective against typhoid bacillus in vitro[14] and in experimental infections.[15] With this agent, although the results of treatment in some patients with typhoid fever seemed encouraging, the results in other patients were quite equivocal.[14]

Of these new agents chloromycetin appears to be more beneficial during the acute illness, but neither of these antibiotics, according to a number of unpublished reports, has any influence on the carrier state.

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STILL THE AMERICAN WAY

Voluntary health insurance needs only time in which to earn the nation's full confidence. By the end of 1948, according to Blue Shield national headquarters, the enrollment in Associated Medical Care Plans had reached 10,370,819, having experienced its greatest quarterly gain, of 1,057,274 members, in the last quarter of the year. This increment represents a growth of 11.35 per cent for the short period mentioned.

Enrolled in this same period were approximately a quarter million Ford Motor Company employees. The majority of these joined Michigan Medical Service, which continues to be the largest plan in the country, with a peak 1948 enrollment of 1,311,811. The New York City Plan ranks second with 1,128,967 members listed.

Varying as Blue Shield plans must in different localities and under a variety of background conditions, there is nevertheless an average or "typical" plan. The average plan is described as providing "complete surgical and obstetrical care including delivery, fractures and dislocations, medical care for hospitalized cases, limited diagnostic x-ray, and anesthesia."

Average subscription costs are $1.17 per month for a single subscriber, who is provided with the above mentioned benefits on a service basis if his annual income is less than $2050, $2.26 for an man and wife and $2.75 for a family. The benefits are provided on a service basis for families with incomes less than $3100.

A criticism directed against voluntary prepayment plans for medical care is that they do not provide complete coverage. This, in fact, should be considered as one of the chief points in their favor. Calculated on an actuarial basis they balance the benefits against the cost, operating on as economical a basis as possible. Like Blue Cross they do not absorb all the costs of illness but cushion the shock, making it possible for the average earner to meet the obligations that have been tempered by his insurance.

Until a real majority of the American people may decide otherwise this form of independence and self-reliance must still be considered as a vital part of the American heritage.

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council of the Massachusetts Medical Society will be held at the Sheraton Hotel, Worcester, on Monday, May 23, 1949, at 7:00 p.m.

Business:

1. Call to order at 7:00 p.m.
2. Presentation of record of meeting held February 2, 1949, as published in *The New England Journal of Medicine*, issue of April 2, 1949.
3. Reports of standing and special committees.
4. Report of Committee on Nominations

   President: DR. ARTHUR W. ALLEN
   President-Elect: DR. LELAND S. MCKITTRICK
   Vice-President: DR. ALBERT A. HORNOR
   Secretary: DR. H. QUIMBY GALLUPE
   Treasurer: DR. ELIOT HUBBARD, JR.
   Assistant Treasurer: DR. NORMAN A. WELCH
   Orator: DR. JOHN W. O'MEARA
5. Such other business as may legally come before this meeting.

Councilors are asked to sign one of the two attendance books before the meeting. The Cotting Supper will be served immediately before the meeting.

H. QUIMBY GALLUPE, M.D.
Secretary

DEATH

CUMMINGS — Morton E. Cummings, M.D., of Malden, died on April 20. He was in his seventy-fourth year.

Dr. Cummings received his degree from Harvard Medical School in 1901.

His widow and a daughter survive.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Abdominal Operations. By Rodney Maingot, F.R.C.S., surgeon to the Royal Free Hospital, London, and to the Southend General Hospital. Second edition, 8°, cloth, 1274 pp., with illustrations. New York: Appleton–Century–Crofts, Incorporated, 1948. $16.00.

This treatise on surgery of the abdomen and its organs is the joint work of Dr. Maingot and eight collaborators. Although the treatise is written by English surgeons, with the exception of Dr. Dragstedt, of the University of Chicago, and Dr. Harrington, of the Mayo Foundation, the book was printed in the United States. The whole text has been thoroughly revised and brought up to date since the publication of the last edition. Many illustrations for new and revised operations have been added. Pertinent references have been interpolated throughout the text. The material is well arranged. A very good, large type has been used, and the illustrations are excellent. The book is recommended for medical libraries and should be available to all persons interested in surgery of the abdomen. It should be recognized as a standard treatise in its field.

Diseases of the Ear, Nose and Throat. By William W. Morrison, M.D., professor of otolaryngology and attending otolaryngologist, New York Polyclinic Medical School and Hospital, senior assistant surgeon in otolaryngology, New York Eye and Ear Infirmary, and associate clinical professor of otolaryngology, New York University College of Medicine. 8°, cloth, 772 pp., with 359 illustrations. New York: Appleton–Century–Crofts, Incorporated, 1948. $8.50.

This new textbook, written for the undergraduate medical student and the general practitioner, is based on a long period of teaching. The text is divided into eight parts. The first is devoted to general considerations, including history taking, equipment for examination and chemotherapy in otolaryngology. The other parts, in order, deal with diseases of the ear, diseases of the external nose and the nasal cavities, allergic diseases of the respiratory tract, and diseases of the paranasal sinuses, of the throat, of the larynx, and of the trachea, bronchi, esophagus and mediastinum. An appendix comprises a formulary of prescriptions for medications to be used by patients. The volume concludes with two indexes of subjects and symptoms. The material is well organized, and the text well written. Lists of selected references are appended to the chapters. The illustrations are original with the author. The book is well published and should prove useful as a reference source.

Streptomycin und Tuberkulose. Herausgegeben von G. Fanconi und W. Löffler unter Mitwirkung von J. Barth et al. 8°, paper, 357 pp., with 233 illustrations. Basel, Switzerland: Benno Schwabe and Company, 1948. 30 Swiss francs.

This monograph is comprehensive and well written. The text is well arranged and consists of introduction and four major sections. The first discusses general problems: influence on cellular respiration, the experimental groundwork, cytotoxic action, and the use of streptomycin, para-aminosalicylic acid and sulfone in experimental tuberculosis. The second deals with hematogenous spreading in tuberculous meningitis, miliary tuberculosis in the aged and in children and tuberculosis in infants and children. The third, comprising about half the text, considers tuberculosis of the various organs and of the lymph nodes, as well as fistulas. The fourth is devoted to the pathological anatomy of tuberculous meningitis and miliary tuberculosis after streptomycin treatment, and a description of 3 cases of osteomalacia occurring in tuberculous meningitis treated with streptomycin. The text is concluded with a large bibliography. The publishing is excellent in every way. There is an adequate table of contents, but the lack of an index detracts from the reference value of the book. The monograph is recommended for all medical libraries and to all persons interested in the subject.

Zinsser's Textbook of Bacteriology: The application of bacteriology and immunology to the diagnosis, specific therapy and prevention of infectious diseases for students and practitioners of medicine and public health. 8°, cloth, 992 pp., with 250 illustrations. Revised by David T. Smith, M.D., professor of bacteriology and associate professor of medicine, Duke University School of Medicine; Donald S. Martin, M.D., M.P.H., professor of preventive medicine and public health and associate professor of bacteriology, Duke University School of Medicine; Norman F. Conant, Ph.D., professor of mycology and associate professor of bacteriology, Duke University School of Medicine; Joseph W. Beard, M.D., professor of surgery in charge of experimental surgery, Duke University School of Medicine; Grant Taylor, M.D., associate professor of bacteriology and associate professor of pediatrics, Duke University School of Medicine; Henry I. Kohn, Ph.D., M.D., surgeon, United States Public Health Service, and assistant professor of physiology and pharmacology (on leave), Duke University School of Medicine; and Mary A. Poston, M.A., instructor in bacteriology, Duke University School of Medicine. Ninth edition. 8°, cloth, 992 pp., with 251 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1948. $10.00.

This standard textbook was first published in 1910. Through eight editions Drs. Hiss, Zinsser and Bayne-Jones were responsible for the text. This edition has been thoroughly revised and brought up to date. The sections on bacterial metabolism, immunology and fungous and viral diseases have been rewritten entirely. A chapter on pleuropneumonia-like organisms and a section on the antibiotics have been added, and the material on the sulfonamides has been expanded.

Likewise, 182 new illustrations, including many electron micrographs, have been included. Lists of pertinent references have been added to the various chapters. A good index concludes the volume. The book is recommended for all medical and public-health libraries and to all persons interested in bacteriology.

NOTICES

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, May 17, at 12 noon. Dr. Francis J. Wenzler will speak on the subject: "Pediatric Aspects of Erythroblastosis and Its Treatment."

Physicians are cordially invited to attend.

VERMONT STATE MEDICAL SOCIETY

The University of Vermont College of Medicine will be host to the Vermont State Medical Society for its annual meeting to be held in Burlington on May 19. The morning session will be held at the Bishop DeGoesbriand Hospital, and lunch and the afternoon sessions will be at the Mary Fletcher Hospital. Papers will be presented by various members of the university faculty.

MASSACHUSETTS GENERAL HOSPITAL

A special research meeting will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Monday, May 23, at 4:30 p.m. Dr. W. F. H. M. Mommaerts, of the Department of Biochemistry, Duke University School of Medicine, will speak on the subject "Fundamental Problems in Muscular and Cardiac Biochemistry."

NEW ENGLAND DIABETES ASSOCIATION

The annual meeting of the New England Diabetes Association will be held in Thayer Hall, City Hospital, Worcester, Massachusetts, on Monday, May 23, at 4 p.m.

CLINICAL PROGRAM

Neuropsychiatric Aspects of Diabetes. Dr. Foster L. Vibber.
Potential Diabetes. Dr. Joseph A. Lundy.
Necrotizing Papillitis in Diabetes. Dr. Edward F. Ramsdell.
Pathology of Necrotizing Papillitis. Dr. Raymond H. Goodale.
Experience with Diabetic Coma at Worcester City Hospital. Dr. Albert E. Hall.
Optimism and Diabetes. Dr. George Ballantyne.

The clinical program will be preceded by the annual business meeting including the election of officers and four directors. This meeting is planned in conjunction with the annual meeting of the Massachusetts Medical Society, May 23 to 26. The meeting will be completed in time so that councilors of the Massachusetts Medical Society can attend the Cotting supper at 6:00 p.m.

CONFERENCE OF PRESIDENTS AND OTHER OFFICERS OF STATE MEDICAL ASSOCIATIONS

The fifth annual Conference of Presidents and Other Officers of State Medical Associations will be held at Atlantic City on Sunday afternoon, June 5. The meeting, which will be held in the Rose Room of the Traymore Hotel on the day preceding the opening of the American Medical Association general sessions, will be open to all physicians. The meeting will be devoted to a discussion of compulsory health insurance plans for medical care and disability compensation.

CONFERENCE OF COUNTY MEDICAL SOCIETY OFFICERS

The fifth national Conference of County Medical Society Officers will be held in the Rose Room of the Hotel Traymore, Atlantic City, on Sunday, June 5. The conference will consist of three panel discussions on emergency calls, local places for medical care of the indigent and the national health campaign. At a session in the Trimble Room of the Claridge Hotel, Atlantic City, at 8 p.m., Mr. Clem Whitaker, director of the National Education Campaign of the American Medical Association, and the Honorable John L. McClellan, United States Senator from Arkansas, will be the speakers.

AMERICAN SOCIETY FOR THE STUDY OF STERILITY

The fifth annual conference of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, on June 6 and 7. The two-day program will be divided into general discussions on the physiology of the uterus, new and known facts concerning reproduction and recent advances in reproduction and a round-table discussion on male sterility.

Additional information may be obtained from the program chairman (Dr. Fred A. Simmons, 330 Dartmouth Street, Boston 16, Massachusetts), the local arrangements chairman (Dr. Abner I. Weisman, 1160 Fifth Avenue, New York City) or the registration secretary (Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield, Massachusetts).

INTERNATIONAL ACADEMY OF PROCTOLOGY

The first meeting of the International Academy of Proctology will be held at the Marlborough-Blenheim in Atlantic City, New Jersey, on Friday, June 10.

The scientific portion of the program will consist of the presentation of papers and motion-picture films of interest to all physicians as well as to those specializing in proctology.

Further information and a copy of the program may be obtained by application to Dr. Alfred J. Cantor, International Academy of Proctology, 43-55 Kissena Boulevard, Flushing, New York.

SOCIETY MEETINGS AND CONFERENCES

MAY 16-19. American Urological Association. Biltmore Hotel, Los Angeles, California.

MAY 17. South End Medical Club. Notice above.

MAY 18-21. Association for Physical and Mental Rehabilitation. Page 401, issue of March 10.

MAY 18-21. American Orthopaedic Association. Page 702, issue of April 28.

MAY 19. Vermont State Medical Society. Notice above.

MAY 23. Massachusetts General Hospital. Notice above.

MAY 23. New England Diabetes Association. Notice above.

MAY 23-27. American Psychiatric Association. Page 668, issue of April 21.

MAY 24-26. Massachusetts Medical Society. Annual Meeting. Worcester Memorial Auditorium, Worcester.

MAY 24-26. Massachusetts Physicians' Art Association. Page 581, issue of April 7.

MAY 26-28. American Goiter Association. Hotel Loraine, Madison, Wisconsin.

MAY 30-JUNE 3. International Congress on Rheumatic Diseases. Page 800. issue of November 18.

JUNE 1-3. Academy of Neurology. Page 588, issue of April 7.

JUNE 2-5. American College of Chest Physicians. Page 490, issue of March 24.

JUNE 3-5. Christian Medical Society Page xv, issue of April 14.

JUNE 5. Conference of Presidents and Other Officers of State Medical Associations. Notice above.

JUNE 5. Conference of County Medical Society Officers. Notice above.

JUNE 6 and 7. American Society for the Study of Sterility. Notice above.

JUNE 10. International Academy of Proctology. Notice above.

JUNE 20-23. Annual Conference of Health Officers and Public Health Nurses. Page xvii, issue of February 3.

JUNE 20-23. American Society of Medical Technologists. Page 531, issue of March 31.

JUNE 30-JULY 2. American Association of Railway Surgeons. Page 490, issue of March 24.

SEPTEMBER 6-10. American Congress of Physical Medicine. Page xii, issue of March 24.

SEPTEMBER 28-30. Mississippi Valley Medical Society. Page 1068, issue of December 30.

(*Notices concluded on page xv*)